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#### (54) Title: COMPOSITIONS AND METHODS FOR THERAPY AND DIAGNOSIS OF PROSTATE CANCER

#### (57) Abstract

Compositions and methods for the therapy and diagnosis of cancer, such as prostate cancer, are disclosed. Compositions may comprise one or more prostate tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a prostate tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as prostate cancer. Diagnostic methods based on detecting a prostate tumor protein, or mRNA encoding such a protein, in a sample are also provided.

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1

# COMPOSITIONS AND METHODS FOR THERAPY AND DIAGNOSIS OF PROSTATE CANCER

#### TECHNICAL FIELD

The present invention relates generally to therapy and diagnosis of cancer, such as prostate cancer. The invention is more specifically related to polypeptides comprising at least a portion of a prostate tumor protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides may be used in vaccines and pharmaceutical compositions for prevention and treatment of prostate cancer, and for the diagnosis and monitoring of such cancers.

#### BACKGROUND OF THE INVENTION

Prostate cancer is the most common form of cancer among males, with an estimated incidence of 30% in men over the age of 50. Overwhelming clinical evidence shows that human prostate cancer has the propensity to metastasize to bone, and the disease appears to progress inevitably from androgen dependent to androgen refractory status, leading to increased patient mortality. This prevalent disease is currently the second leading cause of cancer death among men in the U.S.

In spite of considerable research into therapies for the disease, prostate cancer remains difficult to treat. Commonly, treatment is based on surgery and/or radiation therapy, but these methods are ineffective in a significant percentage of cases. Two previously identified prostate specific proteins - prostate specific antigen (PSA) and prostatic acid phosphatase (PAP) - have limited therapeutic and diagnostic potential. For example, PSA levels do not always correlate well with the presence of prostate cancer, being positive in a percentage of non-prostate cancer cases, including benign prostatic hyperplasia (BPH). Furthermore, PSA measurements correlate with prostate volume, and do not indicate the level of metastasis.

In spite of considerable research into therapies for these and other cancers, prostate cancer remains difficult to diagnose and treat effectively. Accordingly, there is a need in the art for improved methods for detecting and treating such cancers. The present invention fulfills these needs and further provides other related advantages.

#### SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compositions and methods for the diagnosis and therapy of cancer, such as prostate cancer. In one aspect, the present invention provides polypeptides comprising at least a portion of a prostate tumor protein, or a variant thereof. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises at least an immunogenic portion of a prostate tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of: (a) sequences recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472; (b) sequences that hybridize to any of the foregoing sequences under moderately stringent conditions; and (c) complements of any of the sequence of (a) or (b). In certain specific embodiments, such a polypeptide comprises at least a portion, or variant thereof, of a tumor protein that includes an amino acid sequence selected from the group consisting of sequences recited in any one of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380 and 383.

The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least 15 amino acid residues of a prostate tumor protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, vaccines are provided. Such vaccines comprise a polypeptide or polynucleotide as described above and a non-specific immune response enhancer.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a prostate tumor protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, vaccines are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a non-specific immune response enhancer.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Vaccines are further provided, within other aspects, that comprise a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a non-specific immune response enhancer.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition or vaccine as recited above.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a prostate tumor protein, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a prostate tumor protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polypucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of a prostate tumor protein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be prostate cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic

kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

### BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Figure 1 illustrates the ability of T cells to kill fibroblasts expressing the representative prostate tumor polypeptide P502S, as compared to control fibroblasts. The percentage lysis is shown as a series of effector:target ratios, as indicated.

Figures 2A and 2B illustrate the ability of T cells to recognize cells expressing the representative prostate tumor polypeptide P502S. In each case, the number of  $\gamma$ -interferon spots is shown for different numbers of responders. In Figure 2A, data is presented for fibroblasts pulsed with the P2S-12 peptide, as compared to fibroblasts pulsed with a control E75 peptide. In Figure 2B, data is presented for fibroblasts expressing P502S, as compared to fibroblasts expressing HER-2/neu.

Figure 3 represents a peptide competition binding assay showing that the P1S#10 peptide, derived from P501S, binds HLA-A2. Peptide P1S#10 inhibits HLA-A2 restricted presentation of fluM58 peptide to CTL clone D150M58 in TNF release bioassay. D150M58 CTL is specific for the HLA-A2 binding influenza matrix peptide fluM58.

Figure 4 illustrates the ability of T cell lines generated from P1S#10 immunized mice to specifically lyse P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat A2Kb targets, as compared to EGFP-transduced Jurkat A2Kb. The percent lysis is shown as a series of effector to target ratios, as indicated.

Figure 5 illustrates the ability of a T cell clone to recognize and specifically lyse Jurkat A2Kb cells expressing the representative prostate tumor polypeptide P501S, thereby demonstrating that the P1S#10 peptide may be a naturally processed epitope of the P501S polypeptide.

Figures 6A and 6B are graphs illustrating the specificity of a CD8<sup>+</sup> cell line (3A-1) for a representative prostate tumor antigen (P501S). Figure 6A shows the results of a <sup>51</sup>Cr release assay. The percent specific lysis is shown as a series of effector:target ratios, as indicated. Figure 6B shows the production of interferon-gamma by 3A-1 cells stimulated with autologous B-LCL transduced with P501S, at varying effector:target rations as indicated.

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SEQ ID NO: 187 is the determined extended cDNA sequence for 1H-4796 SEQ ID NO: 188 is the determined extended cDNA sequence for 1I-4807 SEQ ID NO: 189 is the determined 3' cDNA sequence for 1I-4810 SEQ ID NO: 190 is the determined 3' cDNA sequence for 1I-4811 SEQ ID NO: 191 is the determined extended cDNA sequence for 1J-4876 SEQ ID NO: 192 is the determined extended cDNA sequence for 1K-4884 SEQ ID NO: 193 is the determined extended cDNA sequence for 1K-4896 SEQ ID NO: 194 is the determined extended cDNA sequence for 1G-4761 SEQ ID NO: 195 is the determined extended cDNA sequence for 1G-4762 SEQ ID NO: 196 is the determined extended cDNA sequence for 1H-4766 SEQ ID NO: 197 is the determined 3' cDNA sequence for 1H-4770 SEQ ID NO: 198 is the determined 3' cDNA sequence for 1H-4771 SEQ ID NO: 199 is the determined extended cDNA sequence for 1H-4772 SEQ ID NO: 200 is the determined extended cDNA sequence for 1D-4309 SEQ ID NO: 201 is the determined extended cDNA sequence for 1D.1-4278 SEQ ID NO: 202 is the determined extended cDNA sequence for 1D-4288 SEQ ID NO: 203 is the determined extended cDNA sequence for 1D-4283 SEQ ID NO: 204 is the determined extended cDNA sequence for 1D-4304 SEQ ID NO: 205 is the determined extended cDNA sequence for 1D-4296 SEQ ID NO: 206 is the determined extended cDNA sequence for 1D-4280 SEQ ID NO: 207 is the determined cDNA sequence for 10-d8fwd SEQ ID NO: 208 is the determined cDNA sequence for 10-H10con SEQ ID NO: 209 is the determined cDNA sequence for 11-C8rev SEQ ID NO: 210 is the determined cDNA sequence for 7.g6fwd SEQ ID NO: 211 is the determined cDNA sequence for 7.g6rev SEQ ID NO: 212 is the determined cDNA sequence for 8-b5fwd SEQ ID NO: 213 is the determined cDNA sequence for 8-b5rev SEQ ID NO: 214 is the determined cDNA sequence for 8-b6fwd SEQ ID NO: 215 is the determined cDNA sequence for 8-b6 rev SEQ ID NO: 216 is the determined cDNA sequence for 8-d4fwd SEQ ID NO: 217 is the determined cDNA sequence for 8-d9rev SEQ ID NO: 218 is the determined cDNA sequence for 8-g3fwd SEQ ID NO: 219 is the determined cDNA sequence for 8-g3rev SEQ ID NO: 220 is the determined cDNA sequence for 8-h11rev SEQ ID NO: 221 is the determined cDNA sequence for g-f12fwd SEQ ID NO: 222 is the determined cDNA sequence for g-f3rev SEQ ID NO: 223 is the determined cDNA sequence for P509S

WO 00/04149 PCT/US99/15838

SEQ ID NO: 224 is the determined cDNA sequence for P510S SEQ ID NO: 225 is the determined cDNA sequence for P703DE5 SEQ ID NO: 226 is the determined cDNA sequence for 9-A11 SEQ ID NO: 227 is the determined cDNA sequence for 8-C6 SEQ ID NO: 228 is the determined cDNA sequence for 8-H7 SEQ ID NO: 229 is the determined cDNA sequence for JPTPN13 SEQ ID NO: 230 is the determined cDNA sequence for JPTPN14 SEQ ID NO: 231 is the determined cDNA sequence for JPTPN23 SEQ ID NO: 232 is the determined cDNA sequence for JPTPN24 SEQ ID NO: 233 is the determined cDNA sequence for JPTPN25 SEQ ID NO: 234 is the determined cDNA sequence for JPTPN30 SEQ ID NO: 235 is the determined cDNA sequence for JPTPN34 SEQ ID NO: 236 is the determined cDNA sequence for PTPN35 SEQ ID NO: 237 is the determined cDNA sequence for JPTPN36 SEQ ID NO: 238 is the determined cDNA sequence for JPTPN38 SEQ ID NO: 239 is the determined cDNA sequence for JPTPN39 SEQ ID NO: 240 is the determined cDNA sequence for JPTPN40 SEQ ID NO: 241 is the determined cDNA sequence for JPTPN41 SEQ ID NO: 242 is the determined cDNA sequence for JPTPN42 SEQ ID NO: 243 is the determined cDNA sequence for JPTPN45 SEQ ID NO: 244 is the determined cDNA sequence for JPTPN46 SEQ ID NO: 245 is the determined cDNA sequence for JPTPN51 SEQ ID NO: 246 is the determined cDNA sequence for JPTPN56 SEQ ID NO: 247 is the determined cDNA sequence for PTPN64 SEQ ID NO: 248 is the determined cDNA sequence for JPTPN65 SEQ ID NO: 249 is the determined cDNA sequence for JPTPN67 SEQ ID NO: 250 is the determined cDNA sequence for JPTPN76 SEQ ID NO: 251 is the determined cDNA sequence for JPTPN84 SEQ ID NO: 252 is the determined cDNA sequence for JPTPN85 SEQ ID NO: 253 is the determined cDNA sequence for JPTPN86 SEQ ID NO: 254 is the determined cDNA sequence for JPTPN87 SEQ ID NO: 255 is the determined cDNA sequence for JPTPN88 SEQ ID NO: 256 is the determined cDNA sequence for JP1F1 SEQ ID NO: 257 is the determined cDNA sequence for JP1F2 SEQ ID NO: 258 is the determined cDNA sequence for JP1C2 SEQ ID NO: 259 is the determined cDNA sequence for JP1B1 SEQ ID NO: 260 is the determined cDNA sequence for JP1B2

WO 00/04149 PCT/US99/15838 ·

SEQ ID NO: 261 is the determined cDNA sequence for JP1D3 SEQ ID NO: 262 is the determined cDNA sequence for JP1A4 SEQ ID NO: 263 is the determined cDNA sequence for JP1F5 SEQ ID NO: 264 is the determined cDNA sequence for JP1E6 SEQ ID NO: 265 is the determined cDNA sequence for JP1D6 SEQ ID NO: 266 is the determined cDNA sequence for JP1B5 SEQ ID NO: 267 is the determined cDNA sequence for JP1A6 SEQ ID NO: 268 is the determined cDNA sequence for JP1E8 SEQ ID NO: 269 is the determined cDNA sequence for JP1D7 SEQ ID NO: 270 is the determined cDNA sequence for JP1D9 SEQ ID NO: 271 is the determined cDNA sequence for JP1C10 SEQ ID NO: 272 is the determined cDNA sequence for JP1A9 SEQ ID NO: 273 is the determined cDNA sequence for JP1F12 SEQ ID NO: 274 is the determined cDNA sequence for JP1E12 SEQ ID NO: 275 is the determined cDNA sequence for JP1D11 SEQ ID NO: 276 is the determined cDNA sequence for JP1C11 SEQ ID NO: 277 is the determined cDNA sequence for JP1C12 SEQ ID NO: 278 is the determined cDNA sequence for JP1B12 SEQ ID NO: 279 is the determined cDNA sequence for JP1A12 SEQ ID NO: 280 is the determined cDNA sequence for JP8G2 SEQ ID NO: 281 is the determined cDNA sequence for JP8H1 SEQ ID NO: 282 is the determined cDNA sequence for JP8H2 SEQ ID NO: 283 is the determined cDNA sequence for JP8A3 SEQ ID NO: 284 is the determined cDNA sequence for JP8A4 SEQ ID NO: 285 is the determined cDNA sequence for JP8C3 SEQ ID NO: 286 is the determined cDNA sequence for JP8G4 SEQ ID NO: 287 is the determined cDNA sequence for JP8B6 SEQ ID NO: 288 is the determined cDNA sequence for JP8D6 SEQ ID NO: 289 is the determined cDNA sequence for JP8F5 SEQ ID NO: 290 is the determined cDNA sequence for JP8A8 SEQ ID NO: 291 is the determined cDNA sequence for JP8C7 SEQ ID NO: 292 is the determined cDNA sequence for JP8D7 SEQ ID NO: 293 is the determined cDNA sequence for P8D8 SEQ ID NO: 294 is the determined cDNA sequence for JP8E7 SEQ ID NO: 295 is the determined cDNA sequence for JP8F8 SEQ ID NO: 296 is the determined cDNA sequence for JP8G8 SEQ ID NO: 297 is the determined cDNA sequence for JP8B10

SEQ ID NO: 298 is the determined cDNA sequence for JP8C10 SEQ ID NO: 299 is the determined cDNA sequence for JP8E9 SEQ ID NO: 300 is the determined cDNA sequence for JP8E10 SEQ ID NO: 301 is the determined cDNA sequence for JP8F9 SEQ ID NO: 302 is the determined cDNA sequence for JP8H9 SEQ ID NO: 303 is the determined cDNA sequence for JP8C12 SEQ ID NO: 304 is the determined cDNA sequence for JP8E11 SEQ ID NO: 305 is the determined cDNA sequence for JP8E12 SEQ ID NO: 306 is the amino acid sequence for the peptide PS2#12 SEQ ID NO: 307 is the determined cDNA sequence for P711P SEQ ID NO: 308 is the determined cDNA sequence for P712P SEQ ID NO: 309 is the determined cDNA sequence for CLONE23 SEQ ID NO: 310 is the determined cDNA sequence for P774P SEQ ID NO: 311 is the determined cDNA sequence for P775P SEQ ID NO: 312 is the determined cDNA sequence for P715P SEQ ID NO: 313 is the determined cDNA sequence for P710P SEQ ID NO: 314 is the determined cDNA sequence for P767P SEQ ID NO: 315 is the determined cDNA sequence for P768P SEQ ID NO: 316-325 are the determined cDNA sequences of previously isolated genes SEQ ID NO: 326 is the determined cDNA sequence for P703PDE5 SEQ ID NO: 327 is the predicted amino acid sequence for P703PDE5 SEQ ID NO: 328 is the determined cDNA sequence for P703P6.26 SEQ ID NO: 329 is the predicted amino acid sequence for P703P6.26 SEQ ID NO: 330 is the determined cDNA sequence for P703PX-23 SEQ ID NO: 331 is the predicted amino acid sequence for P703PX-23 SEQ ID NO: 332 is the determined full length cDNA sequence for P509S SEQ ID NO: 333 is the determined extended cDNA sequence for P707P (also referred to as 11-C9) SEQ ID NO: 334 is the determined cDNA sequence for P714P SEQ ID NO: 335 is the determined cDNA sequence for P705P (also referred to as 9-F3) SEQ ID NO: 336 is the predicted amino acid sequence for P705P SEQ ID NO: 337 is the amino acid sequence of the peptide P1S#10 SEQ ID NO: 338 is the amino acid sequence of the peptide p5 SEQ ID NO: 339 is the predicted amino acid sequence of P509S SEQ ID NO: 340 is the determined cDNA sequence for P778P SEQ ID NO: 341 is the determined cDNA sequence for P786P SEQ ID NO: 342 is the determined cDNA sequence for P789P

WO 00/04149 PCT/US99/15838

SEQ ID NO: 343 is the determined cDNA sequence for a clone showing homology to Homo sapiens MM46 mRNA

SEQ ID NO: 344 is the determined cDNA sequence for a clone showing homology to Homo sapiens TNF-alpha stimulated ABC protein (ABC50) mRNA

SEQ ID NO: 345 is the determined cDNA sequence for a clone showing homology to Homo sapiens mRNA for E-cadherin

SEQ ID NO: 346 is the determined cDNA sequence for a clone showing homology to Human nuclear-encoded mitochondrial serine hydroxymethyltransferase (SHMT)

SEQ ID NO: 347 is the determined cDNA sequence for a clone showing homology to Homo sapiens natural resistance-associated macrophage protein2 (NRAMP2)

SEQ ID NO: 348 is the determined cDNA sequence for a clone showing homology to Homo sapiens phosphoglucomutase-related protein (PGMRP)

SEQ ID NO: 349 is the determined cDNA sequence for a clone showing homology to Human mRNA for proteosome subunit p40

SEQ ID NO: 350 is the determined cDNA sequence for P777P

SEQ ID NO: 351 is the determined cDNA sequence for P779P

SEQ ID NO: 352 is the determined cDNA sequence for P790P

SEQ ID NO: 353 is the determined cDNA sequence for P784P

SEQ ID NO: 354 is the determined cDNA sequence for P776P

SEQ ID NO: 355 is the determined cDNA sequence for P780P

SEQ ID NO: 356 is the determined cDNA sequence for P544S

SEQ ID NO: 357 is the determined cDNA sequence for P745S

SEQ ID NO: 358 is the determined cDNA sequence for P782P

SEQ ID NO: 359 is the determined cDNA sequence for P783P

SEQ ID NO: 360 is the determined cDNA sequence for unknown 17984

SEQ ID NO: 361 is the determined cDNA sequence for P787P

SEQ ID NO: 362 is the determined cDNA sequence for P788P

SEQ ID NO: 363 is the determined cDNA sequence for unknown 17994

SEQ ID NO: 364 is the determined cDNA sequence for P781P

SEQ ID NO: 365 is the determined cDNA sequence for P785P

SEQ ID NO: 366-375 are the determined cDNA sequences for splice variants of B305D.

SEQ ID NO: 376 is the predicted amino acid sequence encoded by the sequence of SEQ ID

NO: 366.

SEQ ID NO: 377 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 372.

SEQ ID NO: 378 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 373.

SEQ ID NO: 379 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 374.

SEQ ID NO: 380 is the predicted amino acid sequence encoded by the sequence of SEQ ID

NO: 375.

SEQ ID NO: 381 is the determined cDNA sequence for B716P.

SEQ ID NO: 382 is the determined full-length cDNA sequence for P711P.

SEQ ID NO: 383 is the predicted amino acid sequence for P711P.

SEQ ID NO: 384 is the cDNA sequence for P1000C.

SEQ ID NO: 385 is the cDNA sequence for CGI-82.

SEQ ID NO:386 is the cDNA sequence for 23320.

SEQ ID NO:387 is the cDNA sequence for CGI-69.

SEQ ID NO:388 is the cDNA sequence for L-iditol-2-dehydrogenase.

SEQ ID NO:389 is the cDNA sequence for 23379.

SEQ ID NO:390 is the cDNA sequence for 23381.

SEQ ID NO:391 is the cDNA sequence for KIAA0122.

SEQ ID NO:392 is the cDNA sequence for 23399.

SEQ ID NO:393 is the cDNA sequence for a previously identified gene.

SEQ ID NO:394 is the cDNA sequence for HCLBP.

SEQ ID NO:395 is the cDNA sequence for transglutaminase.

SEQ ID NO:396 is the cDNA sequence for a previously identified gene.

SEQ ID NO:397 is the cDNA sequence for PAP.

SEQ ID NO:398 is the cDNA sequence for Ets transcription factor PDEF.

SEQ ID NO:399 is the cDNA sequence for hTGR.

SEQ ID NO:400 is the cDNA sequence for KIAA0295.

SEQ ID NO:401 is the cDNA sequence for 22545.

SEQ ID NO:402 is the cDNA sequence for 22547.

SEQ ID NO:403 is the cDNA sequence for 22548.

SEQ ID NO:404 is the cDNA sequence for 22550.

SEQ ID NO:405 is the cDNA sequence for 22551.

SEQ ID NO:406 is the cDNA sequence for 22552.

SEQ ID NO:407 is the cDNA sequence for 22553.

SEQ ID NO:408 is the cDNA sequence for 22558.

SEQ ID NO:409 is the cDNA sequence for 22562.

SEQ ID NO:410 is the cDNA sequence for 22565.

SEQ ID NO:411 is the cDNA sequence for 22567.

SEQ ID NO:412 is the cDNA sequence for 22568.

SEQ ID NO:413 is the cDNA sequence for 22570.

SEQ ID NO:414 is the cDNA sequence for 22571. SEQ ID NO:415 is the cDNA sequence for 22572. SEQ ID NO:416 is the cDNA sequence for 22573. SEQ ID NO:417 is the cDNA sequence for 22573. SEQ ID NO:418 is the cDNA sequence for 22575. SEQ ID NO:419 is the cDNA sequence for 22580. SEQ ID NO:420 is the cDNA sequence for 22581. SEQ ID NO:421 is the cDNA sequence for 22582. SEQ ID NO:422 is the cDNA sequence for 22583. SEQ ID NO:423 is the cDNA sequence for 22584. SEQ ID NO:424 is the cDNA sequence for 22585. SEQ ID NO:425 is the cDNA sequence for 22586. SEQ ID NO:426 is the cDNA sequence for 22587. SEQ ID NO:427 is the cDNA sequence for 22588. SEQ ID NO:428 is the cDNA sequence for 22589. SEQ ID NO:429 is the cDNA sequence for 22590. SEQ ID NO:430 is the cDNA sequence for 22591. SEQ ID NO:431 is the cDNA sequence for 22592. SEQ ID NO:432 is the cDNA sequence for 22593. SEQ ID NO:433 is the cDNA sequence for 22594. SEQ ID NO:434 is the cDNA sequence for 22595. SEQ ID NO:435 is the cDNA sequence for 22596. SEQ ID NO:436 is the cDNA sequence for 22847. SEQ ID NO:437 is the cDNA sequence for 22848. SEQ ID NO:438 is the cDNA sequence for 22849. SEQ ID NO:439 is the cDNA sequence for 22851. SEQ ID NO:440 is the cDNA sequence for 22852. SEQ ID NO:441 is the cDNA sequence for 22853. SEQ ID NO:442 is the cDNA sequence for 22854. SEQ ID NO:443 is the cDNA sequence for 22855. SEQ ID NO:444 is the cDNA sequence for 22856. SEQ ID NO:445 is the cDNA sequence for 22857. SEQ ID NO:446 is the cDNA sequence for 23601. SEQ ID NO:447 is the cDNA sequence for 23602. SEQ ID NO:448 is the cDNA sequence for 23605. SEQ ID NO:449 is the cDNA sequence for 23606. SEQ ID NO:450 is the cDNA sequence for 23612.

SEQ ID NO:451 is the cDNA sequence for 23614.

SEQ ID NO:452 is the cDNA sequence for 23618.

SEQ ID NO:453 is the cDNA sequence for 23622.

SEQ ID NO:454 is the cDNA sequence for folate hydrolase.

SEQ ID NO:455 is the cDNA sequence for LIM protein.

SEQ ID NO:456 is the cDNA sequence for a known gene.

SEQ ID NO:457 is the cDNA sequence for a known gene.

SEQ ID NO:458 is the cDNA sequence for a previously identified gene.

SEQ ID NO:459 is the cDNA sequence for 23045.

SEQ ID NO:460 is the cDNA sequence for 23032.

SEQ ID NO:461 is the cDNA sequence for 23054.

SEQ ID NOs:462-467 are cDNA sequences for known genes.

SEQ ID NOs:468-471 are cDNA sequences for P710P.

SEQ ID NO:472 is a cDNA sequence for P1001C.

## DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy and diagnosis of cancer, such as prostate cancer. compositions described herein may include prostate tumor polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (e.g., T cells). Polypeptides of the present invention generally comprise at least a portion (such as an immunogenic portion) of a prostate tumor protein or a variant thereof. A "prostate tumor protein" is a protein that is expressed in prostate tumor cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in a normal tissue, as determined using a representative assay provided herein. Certain prostate tumor proteins are tumor proteins that react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with prostate cancer. Polynucleotides of the subject invention generally comprise a DNA or RNA sequence that encodes all or a portion of such a polypeptide, or that is complementary to such a sequence. Antibodies are generally immune system proteins, or antigen-binding fragments thereof, that are capable of binding to a polypeptide as described above. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B-cells that express a polypeptide as described above. T cells that may be employed within such compositions are generally T cells that are specific for a polypeptide as described above.

The present invention is based on the discovery of human prostate tumor proteins. Sequences of polynucleotides encoding certain tumor proteins, or portions thereof, are provided in SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472. Sequences of polypeptides comprising at least a portion of a tumor protein are provided in SEQ ID NOs:112-114, 172, 176, 178, 327, 329,

19

#### PROSTATE TUMOR PROTEIN POLYNUCLEOTIDES

331, 336, 339, 376-380 and 383.

Any polynucleotide that encodes a prostate tumor protein or a portion or other variant thereof as described herein is encompassed by the present invention. Preferred polynucleotides comprise at least 15 consecutive nucleotides, preferably at least 30 consecutive nucleotides and more preferably at least 45 consecutive nucleotides, that encode a portion of a prostate tumor protein. More preferably, a polynucleotide encodes an immunogenic portion of a prostate tumor protein. Polynucleotides complementary to any such sequences are also encompassed by the present invention. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (i.e., an endogenous sequence that encodes a prostate tumor protein or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native prostate tumor protein or a portion thereof.

Two polynucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50,

in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 Methods in Enzymology vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) CABIOS 5:151-153; Myers, E.W. and Muller W. (1988) CABIOS 4:11-17; Robinson, E.D. (1971) Comb. Theor 11:105; Santou, N. Nes, M. (1987) Mol. Biol. Evol. 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) Proc. Natl. Acad., Sci. USA 80:726-730.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding a native prostate tumor protein (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to

the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Polynucleotides may be prepared using any of a variety of techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (i.e., expression that is at least five fold greater in a prostate tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, polypeptides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as prostate tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion may be used to isolate a full length gene from a suitable library (e.g., a prostate tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with <sup>32</sup>P) using well known techniques. A bacterial or bacteriophage library is then screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using

WO 00/04149

standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences are then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (see Triglia et al., Nucl. Acids Res. 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., PCR Methods Applic. 1:111-19, 1991) and walking PCR (Parker et al., Nucl. Acids. Res. 19:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence.

Certain nucleic acid sequences of cDNA molecules encoding at least a portion of a prostate tumor protein are provided in SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472. Isolation of these

polynucleotides is described below. Each of these prostate tumor proteins was overexpressed in prostate tumor tissue.

Polynucleotide variants may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis. Modifications in a polynucleotide sequence may also be introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (see Adelman et al., DNA 2:183, 1983). Alternatively, RNA molecules may be generated by in vitro or in vivo transcription of DNA sequences encoding a prostate tumor protein, or portion thereof, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Certain portions may be used to prepare an encoded polypeptide, as described herein. In addition, or alternatively, a portion may be administered to a patient such that the encoded polypeptide is generated in vivo (e.g., by transfecting antigen-presenting cells, such as dendritic cells, with a cDNA construct encoding a prostate tumor polypeptide, and administering the transfected cells to the patient).

A portion of a sequence complementary to a coding sequence (i.e., an antisense polynucleotide) may also be used as a probe or to modulate gene expression. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells of tissues to facilitate the production of antisense RNA. An antisense polynucleotide may be used, as described herein, to inhibit expression of a tumor protein. Antisense technology can be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (see Gee et al., In Huber and Carr, Molecular and Immunologic Approaches, Futura Publishing Co. (Mt. Kisco, NY; 1994)). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (e.g., promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes.

A portion of a coding sequence, or of a complementary sequence, may also be designed as a probe or primer to detect gene expression. Probes may be labeled with a variety of reporter groups, such as radionuclides and enzymes, and are preferably at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length. Primers, as noted above, are preferably 22-30 nucleotides in length.

Any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such

as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Such formulations are particularly useful for therapeutic purposes, as described below. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (e.g., avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

### PROSTATE TUMOR POLYPEPTIDES

Within the context of the present invention, polypeptides may comprise at least an immunogenic portion of a prostate tumor protein or a variant thereof, as described herein. As noted above, a "prostate tumor protein" is a protein that is expressed by prostate tumor cells. Proteins that are prostate tumor proteins also react detectably within an immunoassay (such as an ELISA) with antisera from a patient with prostate cancer. Polypeptides as described herein may be of any length. Additional sequences derived from

the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of a protein that is recognized (i.e., specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a prostate tumor protein or a variant thereof. Certain preferred immunogenic portions include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal deletion (e.g., 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, Fundamental Immunology, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (i.e., they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. An immunogenic portion of a native prostate tumor protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (e.g., in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, 125I-labeled Protein A.

As noted above, a composition may comprise a variant of a native prostate tumor protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native prostate tumor protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigen-specific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein.

WO 00/04149

Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (e.g., 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein. Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity (determined as described above) to the identified polypeptides.

Preferably, a variant contains conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are

WO 00/04149

E. coli, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into

the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., Gene 40:39-46, 1985; Murphy et al., Proc. Natl. Acad. Sci. USA 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. New Engl. J. Med., 336:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (e.g., the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in E. coli (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from Streptococcus pneumoniae, which synthesizes an N-acetyl-L-alanine amidase known as

amidase LYTA (encoded by the LytA gene; Gene 43:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of E. coli C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (see Biotechnology 10:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

#### BINDING AGENTS

The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to a prostate tumor protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a prostate tumor protein if it reacts at a detectable level (within, for example, an ELISA) with a prostate tumor protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10<sup>3</sup> L/mol. The binding constant may be determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as prostate cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a prostate tumor protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (e.g., blood, sera, urine and/or tumor biopsies) from

patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, Eur. J. Immunol. 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient

WO 00/04149

time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include <sup>90</sup>Y, <sup>123</sup>I, <sup>125</sup>I, <sup>131</sup>I, <sup>186</sup>Re, <sup>188</sup>Re, <sup>211</sup>At, and <sup>212</sup>Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and

thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, e.g., U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

#### T CELLS

Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for a prostate tumor protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the CEPRATE™ system, available from CellPro Inc., Bothell WA (*see also* U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a prostate tumor polypeptide, polynucleotide encoding a prostate tumor polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, a prostate tumor polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a prostate tumor polypeptide if the T cells kill target cells coated with the polypeptide or expressing a gene encoding the T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., Cancer Res. 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a prostate tumor polypeptide (100 ng/ml - 100 µg/ml, preferably 200 ng/ml - 25 µg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-y) is indicative of T cell activation (see Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience

(Greene 1998)). T cells that have been activated in response to a prostate tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4<sup>+</sup> and/or CD8<sup>+</sup>. Prostate tumor protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from either a patient or a related, or unrelated, donor and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4<sup>+</sup> or CD8<sup>+</sup> T cells that proliferate in response to a prostate tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a prostate tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a prostate tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of a prostate tumor protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

## PHARMACEUTICAL COMPOSITIONS AND VACCINES

Within certain aspects, polypeptides, polynucleotides, T cells and/or binding agents disclosed herein may be incorporated into pharmaceutical compositions or immunogenic compositions (i.e., vaccines). Pharmaceutical compositions comprise one or more such compounds and a physiologically acceptable carrier. Vaccines may comprise one or more such compounds and a non-specific immune response enhancer. A non-specific immune response enhancer may be any substance that enhances an immune response to an exogenous antigen. Examples of non-specific immune response enhancers include adjuvants, biodegradable microspheres (e.g., polylactic galactide) and liposomes (into which the compound is incorporated; see e.g., Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and vaccines within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition or vaccine.

A pharmaceutical composition or vaccine may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems* 15:143-198, 1998,

and references cited therein. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as Bacillus-Calmette-Guerrin) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., Proc. Natl. Acad. Sci. USA 86:317-321, 1989; Flexner et al., Ann. N.Y. Acad. Sci. 569:86-103, 1989; Flexner et al., Vaccine 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, Biotechniques 6:616-627, 1988; Rosenfeld et al., Science 252:431-434, 1991; Kolls et al., Proc. Natl. Acad. Sci. USA 91:215-219, 1994; Kass-Eisler et al., Proc. Natl. Acad. Sci. USA 90:11498-11502, 1993; Guzman et al., Circulation 88:2838-2848, 1993; and Guzman et al., Cir. Res. 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., Science 259:1745-1749, 1993 and reviewed by Cohen, Science 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Such compositions may also comprise buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide) and/or

PCT/US99/15838

preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of non-specific immune response enhancers may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, Bortadella pertussis or Mycobacterium tuberculosis derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the vaccines provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN-γ, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6, IL-10 and TNF-β) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, Ann. Rev. Immunol. 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Ribi ImmunoChem Research Inc. (Hamilton, MT; see US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555. Another preferred adjuvant is a saponin, preferably QS21, which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is

quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprises an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210. Any vaccine provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient.

The compositions described herein may be administered as part of a sustained release formulation (*i.e.*, a formulation such as a capsule or sponge that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and vaccines to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med. 50*:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*) and based on the lack of differentiation markers of B cells (CD19 and CD20), T cells (CD3), monocytes (CD14) and natural killer cells (CD56), as determined using standard assays. Dendritic cells may, of course, be engineered to express specific cell-

surface receptors or ligands that are not commonly found on dendritic cells in vivo or ex vivo, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (see Zitvogel et al., Nature Med. 4:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcy receptor, mannose receptor and DEC-205 marker. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80 and CD86).

APCs may generally be transfected with a polynucleotide encoding a prostate tumor protein (or portion or other variant thereof) such that the prostate tumor polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place ex vivo, and a composition or vaccine comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs in vivo. In vivo and ex vivo transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., Immunology and cell Biology 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the prostate tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (e.g., vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that

provides T cell help (e.g., a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

#### **CANCER THERAPY**

In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as prostate cancer. Within such methods, pharmaceutical compositions and vaccines are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and vaccines may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides disclosed herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8+ cytotoxic T lymphocytes and CD4+ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein

may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al., Immunological Reviews 157:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated ex vivo for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions disclosed herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (i.e., untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells in vitro. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (e.g., more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to nonvaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 100 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such

a response can be monitored by establishing an improved clinical outcome (e.g., more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a prostate tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

### METHODS FOR DETECTING CANCER

In general, a cancer may be detected in a patient based on the presence of one or more prostate tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as prostate cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a prostate tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding

agent. Suitable polypeptides for use within such assays include full length prostate tumor proteins and portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10  $\mu$ g, and preferably about 100 ng to about 1  $\mu$ g, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with prostate cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20<sup>TM</sup>. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as prostate cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred

embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., Clinical Epidemiology: A Basic Science for Clinical Medicine, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (i.e., sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (i.e., the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use prostate tumor polypeptides to

detect antibodies that bind to such polypeptides in a biological sample. The detection of such prostate tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a prostate tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient is incubated with a prostate tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated in vitro for 2-9 days (typically 4 days) at 37°C with prostate tumor polypeptide (e.g.,  $5 - 25 \mu g/ml$ ). It may be desirable to incubate another aliquot of a T cell sample in the absence of prostate tumor polypeptide to serve as a control. For CD4+ T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8+ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a prostate tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a prostate tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the prostate tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a prostate tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a prostate tumor protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes will hybridize to a polynucleotide encoding a polypeptide disclosed herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers

comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375 and 381. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich ed., PCR Technology, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the disclosed compositions may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple prostate tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

#### DIAGNOSTIC KITS

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a prostate tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a prostate tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a prostate tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a prostate tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

### **EXAMPLES**

### **EXAMPLE 1**

### ISOLATION AND CHARACTERIZATION OF PROSTATE TUMOR POLYPEPTIDES

This Example describes the isolation of certain prostate tumor polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library was constructed from prostate tumor poly A<sup>+</sup> RNA using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD 20897) following the manufacturer's protocol. Specifically, prostate tumor tissues were homogenized with polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A<sup>+</sup> RNA was then purified using a Qiagen oligotex spin column mRNA purification kit (Qiagen, Santa Clarita, CA 91355) according to the manufacturer's protocol. First-strand cDNA was synthesized using the Notl/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with EcoRI/BAXI adaptors (Invitrogen, San Diego, CA) and digested with Notl. Following size fractionation with Chroma Spin-1000 columns (Clontech, Palo Alto, CA), the cDNA was ligated into the EcoRI/Notl site of pCDNA3.1 (Invitrogen) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human pancreas cDNA expression library was prepared from a pool of six tissue specimens (Clontech). The cDNA libraries were characterized by determining the number of independent colonies, the percentage of clones that carried insert, the average insert size and by sequence analysis. The prostate tumor library contained 1.64 x 10<sup>7</sup> independent colonies, with 70% of clones having an insert and the average insert size being 1745 base pairs. The normal pancreas cDNA library contained 3.3 x 10<sup>6</sup> independent colonies, with 69% of clones having inserts and the average insert size being 1120 base pairs. For both libraries, sequence analysis showed that the majority of clones had a full length cDNA sequence and were synthesized from mRNA, with minimal rRNA and mitochondrial DNA contamination.

cDNA library subtraction was performed using the above prostate tumor and normal pancreas cDNA libraries, as described by Hara et al. (Blood, 84:189-199, 1994) with some modifications. Specifically, a prostate tumor-specific subtracted cDNA library was generated as follows. Normal pancreas cDNA library (70 µg) was digested with EcoRI, NotI, and SfuI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 100 µl of

PCT/US99/15838

 $H_2O$ , heat-denatured and mixed with 100  $\mu$ l (100  $\mu$ g) of Photoprobe biotin (Vector Laboratories, Burlingame, CA). As recommended by the manufacturer, the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional Photoprobe biotin (50  $\mu$ l) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23  $\mu$ l  $H_2O$  to form the driver DNA.

To form the tracer DNA, 10 μg prostate tumor cDNA library was digested with BamHI and XhoI, phenol chloroform extracted and passed through Chroma spin-400 columns (Clontech). Following ethanol precipitation, the tracer DNA was dissolved in 5 μl H<sub>2</sub>O. Tracer DNA was mixed with 15 μl driver DNA and 20 μl of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 °C water bath and incubated for 20 hours (long hybridization [LH]). The reaction mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12 μl H<sub>2</sub>O, mixed with 8 μl driver DNA and 20 μl of 2 x hybridization buffer, and subjected to a hybridization at 68 °C for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into BamHI/XhoI site of chloramphenicol resistant pBCSK<sup>+</sup> (Stratagene, La Jolla, CA 92037) and transformed into ElectroMax *E. coli* DH10B cells by electroporation to generate a prostate tumor specific subtracted cDNA library (referred to as "prostate subtraction 1").

To analyze the subtracted cDNA library, plasmid DNA was prepared from 100 independent clones, randomly picked from the subtracted prostate tumor specific library and grouped based on insert size. Representative cDNA clones were further characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A (Foster City, CA). Six cDNA clones, hereinafter referred to as F1-13, F1-12, F1-16, H1-1, H1-9 and H1-4, were shown to be abundant in the subtracted prostate-specific cDNA library. The determined 3' and 5' cDNA sequences for F1-12 are provided in SEQ ID NO: 2 and 3, respectively, with determined 3' cDNA sequences for F1-13, F1-16, H1-1, H1-9 and H1-4 being provided in SEQ ID NO: 1 and 4-7, respectively.

The cDNA sequences for the isolated clones were compared to known sequences in the gene bank using the EMBL and GenBank databases (release 96). Four of the prostate tumor cDNA clones, F1-13, F1-16, H1-1, and H1-4, were determined to encode the following previously identified proteins: prostate specific antigen (PSA), human glandular kallikrein, human tumor expression enhanced gene, and mitochondria cytochrome C oxidase subunit II. H1-9 was found to be identical to a previously identified human

autonomously replicating sequence. No significant homologies to the cDNA sequence for F1-12 were found.

Subsequent studies led to the isolation of a full-length cDNA sequence for F1-12. This sequence is provided in SEQ ID NO: 107, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 108.

To clone less abundant prostate tumor specific genes, cDNA library subtraction was performed by subtracting the prostate tumor cDNA library described above with the normal pancreas cDNA library and with the three most abundant genes in the previously subtracted prostate tumor specific cDNA library: human glandular kallikrein, prostate specific antigen (PSA), and mitochondria cytochrome C oxidase subunit II. Specifically, 1 µg each of human glandular kallikrein, PSA and mitochondria cytochrome C oxidase subunit II cDNAs in pCDNA3.1 were added to the driver DNA and subtraction was performed as described above to provide a second subtracted cDNA library hereinafter referred to as the "subtracted prostate tumor specific cDNA library with spike".

Twenty-two cDNA clones were isolated from the subtracted prostate tumor specific cDNA library with spike. The determined 3' and 5' cDNA sequences for the clones referred to as J1-17, L1-12, N1-1862, J1-13, J1-19, J1-25. J1-24, K1-58, K1-63, L1-4 and L1-14 are provided in SEQ ID NOS: 8-9, 10-11, 12-13, 14-15, 16-17, 18-19, 20-21, 22-23, 24-25, 26-27 and 28-29, respectively. The determined 3' cDNA sequences for the clones referred to as J1-12, J1-16, J1-21, K1-48, K1-55, L1-2, L1-6, N1-1858, N1-1860, N1-1861, N1-1864 are provided in SEQ ID NOS: 30-40, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to three of the five most abundant DNA species, (J1-17, L1-12 and N1-1862; SEQ ID NOS: 8-9, 10-11 and 12-13, respectively). Of the remaining two most abundant species, one (J1-12; SEQ ID NO:30) was found to be identical to the previously identified human pulmonary surfactant-associated protein, and the other (K1-48; SEQ ID NO:33) was determined to have some homology to R. norvegicus mRNA for 2-arylpropionyl-CoA epimerase. Of the 17 less abundant cDNA clones isolated from the subtracted prostate tumor specific cDNA library with spike, four (J1-16, K1-55, L1-6 and N1-1864; SEQ ID NOS:31, 34, 36 and 40, respectively) were found to be identical to previously identified sequences, two (J1-21 and N1-1860; SEQ ID NOS: 32 and 38, respectively) were found to show some homology to non-human sequences, and two (L1-2 and N1-1861; SEQ ID NOS: 35 and 39, respectively) were found to show some homology to known human sequences. No significant homologies were found to the polypeptides J1-13, J1-19, J1-24, J1-25, K1-58, K1-63, L1-4, L1-14 (SEQ ID NOS: 14-15, 16-17, 20-21, 18-19, 22-23, 24-25, 26-27, 28-29, respectively).

Subsequent studies led to the isolation of full length cDNA sequences for J1-17, L1-12 and N1-1862 (SEQ ID NOS: 109-111, respectively). The corresponding predicted

PCT/US99/15838

amino acid sequences are provided in SEQ ID NOS: 112-114. L1-12 is also referred to as P501S.

51

In a further experiment, four additional clones were identified by subtracting a prostate tumor cDNA library with normal prostate cDNA prepared from a pool of three normal prostate poly A+ RNA (referred to as "prostate subtraction 2"). The determined cDNA sequences for these clones, hereinafter referred to as U1-3064, U1-3065, V1-3692 and 1A-3905, are provided in SEQ ID NO: 69-72, respectively. Comparison of the determined sequences with those in the gene bank revealed no significant homologies to U1-3065.

A second subtraction with spike (referred to as "prostate subtraction spike 2") was performed by subtracting a prostate tumor specific cDNA library with spike with normal pancreas cDNA library and further spiked with PSA, J1-17, pulmonary surfactant-associated protein, mitochondrial DNA, cytochrome c oxidase subunit II, N1-1862, autonomously replicating sequence, L1-12 and tumor expression enhanced gene. Four additional clones, hereinafter referred to as V1-3686, R1-2330, 1B-3976 and V1-3679, were isolated. The determined cDNA sequences for these clones are provided in SEQ ID NO:73-76, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to V1-3686 and R1-2330.

Further analysis of the three prostate subtractions described above (prostate subtraction 2, subtracted prostate tumor specific cDNA library with spike, and prostate subtraction spike 2) resulted in the identification of sixteen additional clones, referred to as 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1G-4734, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4810, 1I-4811, 1J-4876, 1K-4884 and 1K-4896. The determined cDNA sequences for these clones are provided in SEQ ID NOS: 77-92, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to 1G-4741, 1G-4734, 1I-4807, 1J-4876 and 1K-4896 (SEQ ID NOS: 79, 81, 87, 90 and 92, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4807, 1J-4876, 1K-4884 and 1K-4896, provided in SEQ ID NOS: 179-188 and 191-193, respectively, and to the determination of additional partial cDNA sequences for 1I-4810 and 1I-4811, provided in SEQ ID NOS: 189 and 190, respectively.

Additional studies with prostate subtraction spike 2 resulted in the isolation of three more clones. Their sequences were determined as described above and compared to the most recent GenBank. All three clones were found to have homology to known genes, which are Cysteine-rich protein, KIAA0242, and KIAA0280 (SEQ ID NO: 317, 319, and 320, respectively). Further analysis of these clones by Synteni microarray (Synteni, Palo Alto, CA) demonstrated that all three clones were over-expressed in most prostate tumors and

prostate BPH, as well as in the majority of normal prostate tissues tested, but low expression in all other normal tissues.

An additional subtraction was performed by subtracting a normal prostate cDNA library with normal pancreas cDNA (referred to as "prostate subtraction 3"). This led to the identification of six additional clones referred to as 1G-4761, 1G-4762, 1H-4766, 1H-4770, 1H-4771 and 1H-4772 (SEQ ID NOS: 93-98). Comparison of these sequences with those in the gene bank revealed no significant homologies to 1G-4761 and 1H-4771 (SEQ ID NOS: 93 and 97, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4761, 1G-4762, 1H-4766 and 1H-4772 provided in SEQ ID NOS: 194-196 and 199, respectively, and to the determination of additional partial cDNA sequences for 1H-4770 and 1H-4771, provided in SEQ ID NOS: 197 and 198, respectively.

Subtraction of a prostate tumor cDNA library, prepared from a pool of polyA+RNA from three prostate cancer patients, with a normal pancreas cDNA library (prostate subtraction 4) led to the identification of eight clones, referred to as 1D-4297, 1D-4309, 1D.1-4278, 1D-4283, 1D-4304, 1D-4296 and 1D-4280 (SEQ ID NOS: 99-107). These sequences were compared to those in the gene bank as described above. No significant homologies were found to 1D-4283 and 1D-4304 (SEQ ID NOS: 103 and 104, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1D-4309, 1D.1-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280, provided in SEQ ID NOS: 200-206, respectively.

cDNA clones isolated in prostate subtraction 1 and prostate subtraction 2, described above, were colony PCR amplified and their mRNA expression levels in prostate tumor, normal prostate and in various other normal tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity. Two clones (referred to as P509S and P510S) were found to be over-expressed in prostate tumor and normal prostate and expressed at low levels in all other normal tissues tested (liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon). The determined cDNA sequences for P509S and P510S are provided in SEQ ID NO: 223 and 224, respectively. Comparison of these sequences with those in the gene bank as described above, revealed some homology to previously identified ESTs.

Additional, studies led to the isolation of the full-length cDNA sequence for P509S. This sequence is provided in SEQ ID NO: 332, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 339.

## EXAMPLE 2 DETERMINATION OF TISSUE SPECIFICITY OF PROSTATE TUMOR POLYPEPTIDES

Using gene specific primers, mRNA expression levels for the representative prostate tumor polypeptides F1-16, H1-1, J1-17 (also referred to as P502S), L1-12 (also referred to as P501S), F1-12 (also referred to as P504S) and N1-1862 (also referred to as P503S) were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent as described above. First strand synthesis was carried out using 1-2  $\mu g$  of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42  $^{o}$ C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR,  $\beta$ -actin was used as an internal control for each of the tissues examined. First, serial dilutions of the first strand cDNAs were prepared and RT-PCR assays were performed using  $\beta$ -actin specific primers. A dilution was then chosen that enabled the linear range amplification of the  $\beta$ -actin template and which was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the  $\beta$ -actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in four different types of tumor tissue (prostate tumor from 2 patients, breast tumor from 3 patients, colon tumor, lung tumor), and sixteen different normal tissues, including prostate, colon, kidney, liver, lung, ovary, pancreas, skeletal muscle, skin, stomach, testes, bone marrow and brain. F1-16 was found to be expressed at high levels in prostate tumor tissue, colon tumor and normal prostate, and at lower levels in normal liver, skin and testes, with expression being undetectable in the other tissues examined. H1-1 was found to be expressed at high levels in prostate tumor, lung tumor, breast tumor, normal prostate, normal colon and normal brain, at much lower levels in normal lung, pancreas, skeletal muscle, skin, small intestine, bone marrow, and was not detected in the other tissues tested. J1-17 (P502S) and L1-12 (P501S) appear to be specifically over-expressed in prostate, with both genes being expressed at high levels in prostate tumor and normal prostate but at low to undetectable levels in all the other tissues examined. N1-1862 (P503S) was found to be over-expressed in 60% of prostate tumors and detectable in normal colon and kidney. The RT-PCR results thus indicate that

F1-16, H1-1, J1-17 (P502S), N1-1862 (P503S) and L1-12 (P501S) are either prostate specific or are expressed at significantly elevated levels in prostate.

Further RT-PCR studies showed that F1-12 (P504S) is over-expressed in 60% of prostate tumors, detectable in normal kidney but not detectable in all other tissues tested. Similarly, R1-2330 was shown to be over-expressed in 40% of prostate tumors, detectable in normal kidney and liver, but not detectable in all other tissues tested. U1-3064 was found to be over-expressed in 60% of prostate tumors, and also expressed in breast and colon tumors, but was not detectable in normal tissues.

RT-PCR characterization of R1-2330, U1-3064 and 1D-4279 showed that these three antigens are over-expressed in prostate and/or prostate tumors.

Northern analysis with four prostate tumors, two normal prostate samples, two BPH prostates, and normal colon, kidney, liver, lung, pancrease, skeletal muscle, brain, stomach, testes, small intestine and bone marrow, showed that L1-12 (P501S) is over-expressed in prostate tumors and normal prostate, while being undetectable in other normal tissues tested. J1-17 (P502S) was detected in two prostate tumors and not in the other tissues tested. N1-1862 (P503S) was found to be over-expressed in three prostate tumors and to be expressed in normal prostate, colon and kidney, but not in other tissues tested. F1-12 (P504S) was found to be highly expressed in two prostate tumors and to be undetectable in all other tissues tested.

The microarray technology described above was used to determine the expression levels of representative antigens described herein in prostate tumor, breast tumor and the following normal tissues: prostate, liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon. L1-12 (P501S) was found to be over-expressed in normal prostate and prostate tumor, with some expression being detected in normal skeletal muscle. Both J1-12 and F1-12 (P504S) were found to be over-expressed in prostate tumor, with expression being lower or undetectable in all other tissues tested. N1-1862 (P503S) was found to be expressed at high levels in prostate tumor and normal prostate, and at low levels in normal large intestine and normal colon, with expression being undetectable in all other tissues tested. R1-2330 was found to be over-expressed in prostate tumor and normal prostate, and to be expressed at lower levels in all other tissues tested. 1D-4279 was found to be over-expressed in prostate tumor and normal spinal cord, and to be undetectable in all other tissues tested.

Further microarray analysis to specifically address the extent to which P501S (SEQ ID NO: 110) was expressed in breast tumor revealed moderate over-expression not only in breast tumor, but also in metastatic breast tumor (2/31), with negligible to low expression

in normal tissues. This data suggests that P501S may be over-expressed in various breast tumors as well as in prostate tumors.

The expression levels of 32 ESTs (expressed sequence tags) described by Vasmatzis et al. (Proc. Natl. Acad. Sci. USA 95:300-304, 1998) in a variety of tumor and normal tissues were examined by microarray technology as described above. Two of these clones (referred to as P1000C and P1001C) were found to be over-expressed in prostate tumor and normal prostate, and expressed at low to undetectable levels in all other tissues tested (normal aorta, thymus, resting and activated PBMC, epithelial cells, spinal cord, adrenal gland, fetal tissues, skin, salivary gland, large intestine, bone marrow, liver, lung, dendritic cells, stomach, lymph nodes, brain, heart, small intestine, skeletal muscle, colon and kidney. The determined cDNA sequences for P1000C and P1001C are provided in SEQ ID NO: 384 and 472, respectively. The sequence of P1001C was found to show some homology to the previously isolated Human mRNA for JM27 protein. No significant homologies were found to the sequence of P1000C.

The expression of the polypeptide encoded by the full length cDNA sequence for F1-12 (also referred to as P504S; SEQ ID NO: 108) was investigated by immunohistochemical analysis. Rabbit-anti-P504S polyclonal antibodies were generated against the full length P504S protein by standard techniques. Subsequent isolation and characterization of the polyclonal antibodies were also performed by techniques well known in the art. Immunohistochemical analysis showed that the P504S polypeptide was expressed in 100% of prostate carcinoma samples tested (n=5).

The rabbit-anti-P504S polyclonal antibody did not appear to label benign prostate cells with the same cytoplasmic granular staining, but rather with light nuclear staining. Analysis of normal tissues revealed that the encoded polypeptide was found to be expressed in some, but not all normal human tissues. Positive cytoplasmic staining with rabbit-anti-P504S polyclonal antibody was found in normal human kidney, liver, brain, colon and lung-associated macrophages, whereas heart and bone marrow were negative.

This data indicates that the P504S polypeptide is present in prostate cancer tissues, and that there are qualitative and quantitative differences in the staining between benign prostatic hyperplasia tissues and prostate cancer tissues, suggesting that this polypeptide may be detected selectively in prostate tumors and therefore be useful in the diagnosis of prostate cancer.

### **EXAMPLE 3**

ISOLATION AND CHARACTERIZATION OF PROSTATE TUMOR POLYPEPTIDES
BY PCR-BASED SUBTRACTION

A cDNA subtraction library, containing cDNA from normal prostate subtracted with ten other normal tissue cDNAs (brain, heart, kidney, liver, lung, ovary, placenta, skeletal muscle, spleen and thymus) and then submitted to a first round of PCR amplification, was purchased from Clontech. This library was subjected to a second round of PCR amplification, following the manufacturer's protocol. The resulting cDNA fragments were subcloned into the vector pT7 Blue T-vector (Novagen, Madison, WI) and transformed into XL-1 Blue MRF' E. coli (Stratagene). DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A.

Fifty-nine positive clones were sequenced. Comparison of the DNA sequences of these clones with those in the gene bank, as described above, revealed no significant homologies to 25 of these clones, hereinafter referred to as P5, P8, P9, P18, P20, P30, P34, P36, P38, P39, P42, P49, P50, P53, P55, P60, P64, P65, P73, P75, P76, P79 and P84. The determined cDNA sequences for these clones are provided in SEQ ID NO: 41-45, 47-52 and 54-65, respectively. P29, P47, P68, P80 and P82 (SEQ ID NO: 46, 53 and 66-68, respectively) were found to show some degree of homology to previously identified DNA sequences. To the best of the inventors' knowledge, none of these sequences have been previously shown to be present in prostate.

Further studies using the PCR-based methodology described above resulted in the isolation of more than 180 additional clones, of which 23 clones were found to show no significant homologies to known sequences. The determined cDNA sequences for these clones are provided in SEQ ID NO: 115-123, 127, 131, 137, 145, 147-151, 153, 156-158 and 160. Twenty-three clones (SEQ ID NO: 124-126, 128-130, 132-136, 138-144, 146, 152, 154, 155 and 159) were found to show some homology to previously identified ESTs. An additional ten clones (SEQ ID NO: 161-170) were found to have some degree of homology to known genes. Larger cDNA clones containing the P20 sequence represent splice variants of a gene referred to as P703P. The determined DNA sequence for the variants referred to as DE1, DE13 and DE14 are provided in SEQ ID NOS: 171, 175 and 177, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 172, 176 and 178, respectively. The determined cDNA sequence for an extended spliced form of P703 is provided in SEQ ID NO: 225. The DNA sequences for the splice variants referred to as DE2 and DE6 are provided in SEQ ID NOS: 173 and 174, respectively.

mRNA Expression levels for representative clones in tumor tissues (prostate (n=5), breast (n=2), colon and lung) normal tissues (prostate (n=5), colon, kidney, liver, lung (n=2), ovary (n=2), skeletal muscle, skin, stomach, small intestine and brain), and activated

PCT/US99/15838 \*\*

and non-activated PBMC was determined by RT-PCR as described above. Expression was examined in one sample of each tissue type unless otherwise indicated.

P9 was found to be highly expressed in normal prostate and prostate tumor compared to all normal tissues tested except for normal colon which showed comparable expression. P20, a portion of the P703P gene, was found to be highly expressed in normal prostate and prostate tumor, compared to all twelve normal tissues tested. A modest increase in expression of P20 in breast tumor (n=2), colon tumor and lung tumor was seen compared to all normal tissues except lung (1 of 2). Increased expression of P18 was found in normal prostate, prostate tumor and breast tumor compared to other normal tissues except lung and stomach. A modest increase in expression of P5 was observed in normal prostate compared to most other normal tissues. However, some elevated expression was seen in normal lung and PBMC. Elevated expression of P5 was also observed in prostate tumors (2 of 5), breast tumor and one lung tumor sample. For P30, similar expression levels were seen in normal prostate and prostate tumor, compared to six of twelve other normal tissues tested. Increased expression was seen in breast tumors, one lung tumor sample and one colon tumor sample, and also in normal PBMC. P29 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to the majority of normal tissues. However, substantial expression of P29 was observed in normal colon and normal lung (2 of 2). P80 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to all other normal tissues tested, with increased expression also being seen in colon tumor.

Further studies resulted in the isolation of twelve additional clones, hereinafter referred to as 10-d8, 10-h10, 11-c8, 7-g6, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3, 8-h11, 9-f12 and 9-f3. The determined DNA sequences for 10-d8, 10-h10, 11-c8, 8-d4, 8-d9, 8-h11, 9-f12 and 9-f3 are provided in SEQ ID NO: 207, 208, 209, 216, 217, 220, 221 and 222, respectively. The determined forward and reverse DNA sequences for 7-g6, 8-b5, 8-b6 and 8-g3 are provided in SEQ ID NO: 210 and 211; 212 and 213; 214 and 215; and 218 and 219, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to the sequence of 9-f3. The clones 10-d8, 11-c8 and 8-h11 were found to show some homology to previously isolated ESTs, while 10-h10, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3 and 9-f12 were found to show some homology to previously identified genes. Further characterization of 7-G6 and 8-G3 showed identity to the known genes PAP and PSA, respectively.

mRNA expression levels for these clones were determined using the micro-array technology described above. The clones 7-G6, 8-G3, 8-B5, 8-B6, 8-D4, 8-D9, 9-F3, 9-F12, 9-H3, 10-A2, 10-A4, 11-C9 and 11-F2 were found to be over-expressed in prostate tumor and normal prostate, with expression in other tissues tested being low or undetectable.

Increased expression of 8-F11 was seen in prostate tumor and normal prostate, bladder, skeletal muscle and colon. Increased expression of 10-H10 was seen in prostate tumor and normal prostate, bladder, lung, colon, brain and large intestine. Increased expression of 9-B1 was seen in prostate tumor, breast tumor, and normal prostate, salivary gland, large intestine and skin, with increased expression of 11-C8 being seen in prostate tumor, and normal prostate and large intestine.

An additional cDNA fragment derived from the PCR-based normal prostate subtraction, described above, was found to be prostate specific by both micro-array technology and RT-PCR. The determined cDNA sequence of this clone (referred to as 9-A11) is provided in SEQ ID NO: 226. Comparison of this sequence with those in the public databases revealed 99% identity to the known gene HOXB13.

Further studies led to the isolation of the clones 8-C6 and 8-H7. The determined cDNA sequences for these clones are provided in SEQ ID NO: 227 and 228, respectively. These sequences were found to show some homology to previously isolated ESTs.

PCR and hybridization-based methodologies were employed to obtain longer cDNA sequences for clone P20 (also referred to as P703P), yielding three additional cDNA fragments that progressively extend the 5' end of the gene. These fragments, referred to as P703PDE5, P703P6.26, and P703PX-23 (SEQ ID NO: 326, 328 and 330, with the predicted corresponding amino acid sequences being provided in SEQ ID NO: 327, 329 and 331, respectively) contain additional 5' sequence: P703PDE5 was recovered by screening of a cDNA library (#141-26) with a portion of P703P as a probe. P703P6.26 was recovered from a mixture of three prostate tumor cDNAs and P703PX\_23 was recovered from cDNA library (#438-48). Together, the additional sequences include all of the putative mature serine protease along with part of the putative signal sequence. Further studies using a PCR-based subtraction library of a prostate tumor pool subtracted against a pool of normal tissues (referred to as JP: PCR subtraction) resulted in the isolation of thirteen additional clones, seven of which did not share any significant homology to known GenBank sequences. The determined cDNA sequences for these seven clones (P711P, P712P, novel 23, P774P, P775P, P710P and P768P) are provided in SEQ ID NO: 307-311, 313 and 315, respectively. The remaining six clones (SEQ ID NO: 316 and 321-325) were shown to share some homology to known genes. By microarray analysis, all thirteen clones showed three or more fold overexpression in prostate tissues, including prostate tumors, BPH and normal prostate as compared to normal non-prostate tissues. Clones P711P, P712P, novel 23 and P768P showed over-expression in most prostate tumors and BPH tissues tested (n=29), and in the majority of normal prostate tissues (n=4), but background to low expression levels in all normal tissues.

Clones P774P, P775P and P710P showed comparatively lower expression and expression in fewer prostate tumors and BPH samples, with negative to low expression in normal prostate.

The full-length cDNA for P711P was obtained by employing the partial sequence of SEQ ID NO: 307 to screen a prostate cDNA library. Specifically, a directionally cloned prostate cDNA library was prepared using standard techniques. One million colonies of this library were plated onto LB/Amp plates. Nylon membrane filters were used to lift these colonies, and the cDNAs which were picked up by these filters were denatured and cross-linked to the filters by UV light. The P711P cDNA fragment of SEQ ID NO: 307 was radio-labeled and used to hybridize with these filters. Positive clones were selected, and cDNAs were prepared and sequenced using an automatic Perkin Elmer/Applied Biosystems sequencer. The determined full-length sequence of P711P is provided in SEQ ID NO: 382, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 383.

Using PCR and hybridization-based methodologies, additional cDNA sequence information was derived for two clones described above, 11-C9 and 9-F3, herein after referred to as P707P and P714P, respectively (SEQ ID NO: 333 and 334). After comparison with the most recent GenBank, P707P was found to be a splice variant of the known gene HoxB13. In contrast, no significant homologies to P714P were found.

Clones 8-B3, P89, P98, P130 and P201 (as disclosed in U.S. Patent Application No. 09/020,956, filed February 9, 1998) were found to be contained within one contiguous sequence, referred to as P705P (SEQ ID NO: 335, with the predicted amino acid sequence provided in SEQ ID NO: 336), which was determined to be a splice variant of the known gene NKX 3.1.

### EXAMPLE 4 SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following

lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

### **EXAMPLE 5**

## FURTHER ISOLATION AND CHARACTERIZATION OF PROSTATE TUMOR POLYPEPTIDES BY PCR-BASED SUBTRACTION

A cDNA library generated from prostate primary tumor mRNA as described above was subtracted with cDNA from normal prostate. The subtraction was performed using a PCR-based protocol (Clontech), which was modified to generate larger fragments. Within this protocol, tester and driver double stranded cDNA were separately digested with five restriction enzymes that recognize six-nucleotide restriction sites (MluI, MscI, PvuII, SalI and StuI). This digestion resulted in an average cDNA size of 600 bp, rather than the average size of 300 bp that results from digestion with RsaI according to the Clontech protocol. This modification did not affect the subtraction efficiency. Two tester populations were then created with different adapters, and the driver library remained without adapters.

The tester and driver libraries were then hybridized using excess driver cDNA. In the first hybridization step, driver was separately hybridized with each of the two tester cDNA populations. This resulted in populations of (a) unhybridized tester cDNAs, (b) tester cDNAs hybridized to other tester cDNAs, (c) tester cDNAs hybridized to driver cDNAs and (d) unhybridized driver cDNAs. The two separate hybridization reactions were then combined, and rehybridized in the presence of additional denatured driver cDNA. Following this second hybridization, in addition to populations (a) through (d), a fifth population (e) was generated in which tester cDNA with one adapter hybridized to tester cDNA with the second adapter. Accordingly, the second hybridization step resulted in enrichment of differentially expressed sequences which could be used as templates for PCR amplification with adaptor-specific primers.

The ends were then filled in, and PCR amplification was performed using adaptor-specific primers. Only population (e), which contained tester cDNA that did not hybridize to driver cDNA, was amplified exponentially. A second PCR amplification step was then performed, to reduce background and further enrich differentially expressed sequences.

This PCR-based subtraction technique normalizes differentially expressed cDNAs so that rare transcripts that are overexpressed in prostate tumor tissue may be recoverable. Such transcripts would be difficult to recover by traditional subtraction methods.

WO 00/04149 PCT/US99/15838

61

In addition to genes known to be overexpressed in prostate tumor, seventy-seven further clones were identified. Sequences of these partial cDNAs are provided in SEQ ID NO: 29 to 305. Most of these clones had no significant homology to database sequences. Exceptions were JPTPN23 (SEQ ID NO: 231; similarity to pig valosin-containing protein), JPTPN30 (SEQ ID NO: 234; similarity to rat mRNA for proteasome subunit), JPTPN45 (SEQ ID NO: 243; similarity to rat norvegicus cytosolic NADP-dependent isocitrate dehydrogenase), JPTPN46 (SEQ ID NO: 244; similarity to human subclone H8 4 d4 DNA sequence), JP1D6 (SEQ ID NO: 265; similarity to G. gallus dynein light chain-A), JP8D6 (SEQ ID NO: 288; similarity to human BAC clone RG016J04), JP8F5 (SEQ ID NO: 289; similarity to human subclone H8 3 b5 DNA sequence), and JP8E9 (SEQ ID NO: 299; similarity to human Alu sequence).

Additional studies using the PCR-based subtraction library consisting of a prostate tumor pool subtracted against a normal prostate pool (referred to as PT-PN PCR subtraction) yielded three additional clones. Comparison of the cDNA sequences of these clones with the most recent release of GenBank revealed no significant homologies to the two clones referred to as P715P and P767P (SEQ ID NO: 312 and 314). The remaining clone was found to show some homology to the known gene KIAA0056 (SEQ ID NO: 318). Using microarray analysis to measure mRNA expression levels in various tissues, all three clones were found to be over-expressed in prostate tumors and BPH tissues. Specifically, clone P715P was over-expressed in most prostate tumors and BPH tissues by a factor of three or greater, with elevated expression seen in the majority of normal prostate samples and in fetal tissue, but negative to low expression in all other normal tissues. Clone P767P was over-expressed in several prostate tumors and BPH tissues, with moderate expression levels in half of the normal prostate samples, and background to low expression in all other normal tissues tested.

Further analysis, by microarray as described above, of the PT-PN PCR subtraction library and of a DNA subtraction library containing cDNA from prostate tumor subtracted with a pool of normal tissue cDNAs, led to the isolation of 27 additional clones (SEQ ID NO: 340-365 and 381) which were determined to be over-expressed in prostate tumor. The clones of SEQ ID NO: 341, 342, 345, 347, 348, 349, 351, 355-359, 361, 362 and 364 were also found to be expressed in normal prostate. Expression of all 26 clones in a variety of normal tissues was found to be low or undetectable, with the exception of P544S (SEQ ID NO: 356) which was found to be expressed in small intestine. Of the 26 clones, 10 (SEQ ID NO: 340-349) were found to show some homology to previously identified sequences. No significant homologies were found to the clones of SEQ ID NO: 350-365.

### EXAMPLE 6 PEPTIDE PRIMING OF MICE AND PROPAGATION OF CTL LINES

6.1. This Example illustrates the preparation of a CTL cell line specific for cells expressing the P502S gene.

Mice expressing the transgene for human HLA A2.1 (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with P2S#12 peptide (VLGWVAEL; SEQ ID NO: 306), which is derived from the P502S gene (also referred to herein as J1-17, SEQ ID NO: 8), as described by Theobald et al., Proc. Natl. Acad. Sci. USA 92:11993-11997, 1995 with the following modifications. Mice were immunized with 100 $\mu g$  of P2S#12 and 120 $\mu g$  of an I-A binding peptide derived from hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and using a nylon mesh single cell suspensions prepared. Cells were then resuspended at 6 x 106 cells/ml in complete media (RPMI-1640; Gibco BRL, Gaithersburg, MD) containing 10% FCS, 2mM Glutamine (Gibco BRL), sodium pyruvate (Gibco BRL), non-essential amino acids (Gibco BRL), 2 x 10<sup>-5</sup> M 2-mercaptoethanol, 50U/ml penicillin and streptomycin, and cultured in the presence of irradiated (3000 rads) P2S#12-pulsed (5mg/ml P2S#12 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7µg/ml dextran sulfate and 25µg/ml LPS for 3 days). Six days later, cells (5 x 105/ml) were restimulated with 2.5 x 106/ml peptide pulsed irradiated (20,000 rads) EL4A2Kb cells (Sherman et al, Science 258:815-818, 1992) and 3 x 106/ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20U/ml IL-2. Cells continued to be restimulated on a weekly basis as described, in preparation for cloning the line.

P2S#12 line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1 x  $10^4$  cells/ well) as stimulators and A2 transgenic spleen cells as feeders (5 x  $10^5$  cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were

restimulated as before. On day 21, clones that were growing were isolated and maintained in culture. Several of these clones demonstrated significantly higher reactivity (lysis) against human fibroblasts (HLA A2.1 expressing) transduced with P502S than against control fibroblasts. An example is presented in Figure 1.

This data indicates that P2S #12 represents a naturally processed epitope of the P502S protein that is expressed in the context of the human HLA A2.1 molecule.

6.2. This Example illustrates the preparation of murine CTL lines and CTL clones specific for cells expressing the P501S gene.

This series of experiments were performed similarly to that described above. Mice were immunized with the P1S#10 peptide (SEQ ID NO: 337), which is derived from the P501S gene (also referred to herein as L1-12, SEQ ID NO: 110). The P1S#10 peptide was derived by analysis of the predicted polypeptide sequence for P501S for potential HLA-A2 binding sequences as defined by published HLA-A2 binding motifs (Parker, KC, et al, J. Immunol., 152:163, 1994). P1S#10 peptide was synthesized as described in Example 4, and empirically tested for HLA-A2 binding using a T cell based competition assay. Predicted A2 binding peptides were tested for their ability to compete HLA-A2 specific peptide presentation to an HLA-A2 restricted CTL clone (D150M58), which is specific for the HLA-A2 binding influenza matrix peptide fluM58. D150M58 CTL secretes TNF in response to self-presentation of peptide fluM58. In the competition assay, test peptides at 100-200 µg/ml were added to cultures of D150M58 CTL in order to bind HLA-A2 on the CTL. After thirty minutes, CTL cultured with test peptides, or control peptides, were tested for their antigen dose response to the fluM58 peptide in a standard TNF bioassay. As shown in Figure 3, peptide P1S#10 competes HLA-A2 restricted presentation of fluM58, demonstrating that peptide P1S#10 binds HLA-A2.

Mice expressing the transgene for human HLA A2.1 were immunized as described by Theobald et al. (*Proc. Natl. Acad. Sci. USA 92*:11993-11997, 1995) with the following modifications. Mice were immunized with 62.5μg of P1S #10 and 120μg of an I-A<sup>b</sup> binding peptide derived from Hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and single cell suspensions prepared using a nylon mesh. Cells were then resuspended at 6 x 10<sup>6</sup> cells/ml in complete media (as described above) and cultured in the presence of irradiated (3000 rads) P1S#10-pulsed (2μ g/ml P1S#10 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7μg/ml dextran sulfate and 25μg/ml LPS for 3 days). Six days later cells (5 x 10<sup>5</sup>/ml) were restimulated with 2.5 x 10<sup>6</sup>/ml peptide-pulsed irradiated (20,000 rads) EL4A2Kb cells, as described above, and 3 x 10<sup>6</sup>/ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20 U/ml IL-2. Cells were restimulated on a weekly

basis in preparation for cloning. After three rounds of *in vitro* stimulations, one line was generated that recognized P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat targets as shown in Figure 4.

A P1S#10-specific CTL line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1 x 10<sup>4</sup> cells/ well) as stimulators and A2 transgenic spleen cells as feeders (5 x 10<sup>5</sup> cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, viable clones were isolated and maintained in culture. As shown in Figure 5, five of these clones demonstrated specific cytolytic reactivity against P501S-transduced Jurkat A2Kb targets. This data indicates that P1S#10 represents a naturally processed epitope of the P501S protein that is expressed in the context of the human HLA-A2.1 molecule.

# EXAMPLE 7 ABILITY OF HUMAN T CELLS TO RECOGNIZE PROSTATE TUMOR POLYPEPTIDES

This Example illustrates the ability of T cells specific for a prostate tumor polypeptide to recognize human tumor.

Human CD8<sup>+</sup> T cells were primed in vitro to the P2S-12 peptide (SEQ ID NO: 306) derived from P502S (also referred to as J1-17) using dendritic cells according to the protocol of Van Tsai et al. (Critical Reviews in Immunology 18:65-75, 1998). The resulting CD8+ T cell microcultures were tested for their ability to recognize the P2S-12 peptide presented by autologous fibroblasts or fibroblasts which were transduced to express the P502S gene in a γ-interferon ELISPOT assay (see Lalvani et al., J. Exp. Med. 186:859-865, 1997). Briefly, titrating numbers of T cells were assayed in duplicate on 104 fibroblasts in the presence of 3  $\mu g/ml$  human  $\beta_2$ -microglobulin and 1  $\mu g/ml$  P2S-12 peptide or control E75 In addition, T cells were simultaneously assayed on autologous fibroblasts transduced with the P502S gene or as a control, fibroblasts transduced with HER-2/neu. Prior to the assay, the fibroblasts were treated with 10 ng/ml  $\gamma$ -interferon for 48 hours to upregulate class I MHC expression. One of the microcultures (#5) demonstrated strong recognition of both peptide pulsed fibroblasts as well as transduced fibroblasts in a  $\gamma$ -interferon ELISPOT assay. Figure 2A demonstrates that there was a strong increase in the number of y-interferon spots with increasing numbers of T cells on fibroblasts pulsed with the P2S-12 peptide (solid bars) but not with the control E75 peptide (open bars). This shows the ability of these T cells to specifically recognize the P2S-12 peptide. As shown in Figure 2B, this microculture also demonstrated an increase in the number of  $\gamma$ -interferon spots with increasing numbers of T

cells on fibroblasts transduced to express the P502S gene but not the HER-2/neu gene. These results provide additional confirmatory evidence that the P2S-12 peptide is a naturally processed epitope of the P502S protein. Furthermore, this also demonstrates that there exists in the human T cell repertoire, high affinity T cells which are capable of recognizing this epitope. These T cells should also be capable of recognizing human tumors which express the P502S gene.

## EXAMPLE 8 PRIMING OF CTL IN VIVO USING NAKED DNA IMMUNIZATION WITH A PROSTATE ANTIGEN

The prostate tumor antigen L1-12, as described above, is also referred to as P501S. HLA A2Kb Tg mice (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with 100 µg VR10132-P501S either intramuscularly or intradermally. The mice were immunized three times, with a two week interval between immunizations. Two weeks after the last immunization, immune spleen cells were cultured with Jurkat A2Kb-P501S transduced stimulator cells. CTL lines were stimulated weekly. After two weeks of *in vitro* stimulation, CTL activity was assessed against P501S transduced targets. Two out of 8 mice developed strong anti-P501S CTL responses. These results demonstrate that P501S contains at least one naturally processed A2-restricted CTL epitope.

### **EXAMPLE 9**

## GENERATION OF HUMAN CTL *IN VITRO* USING WHOLE GENE PRIMING AND STIMULATION TECHNIQUES WITH PROSTATE TUMOR ANTIGEN

Using *in vitro* whole-gene priming with P501S-retrovirally transduced autologous fibroblasts (see, for example, Yee et al, *The Journal of Immunology*, 157(9):4079-86, 1996), human CTL lines were derived that specifically recognize autologous fibroblasts transduced with P501S (also known as L1-12), as determined by interferon-γ ELISPOT analysis as described above. Using a panel of HLA-mismatched fibroblast lines transduced with P501S, these CTL lines were shown to be restricted HLA-A2 class I allele. Specifically, dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by growing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, DC were infected overnight with recombinant P501S vaccinia virus at a multiplicity of infection (M.O.I) of five, and matured overnight by the addition of 3 μg/ml CD40 ligand. Virus was inactivated by UV irradiation. CD8+ T cells were isolated using a magnetic bead system, and

priming cultures were initiated using standard culture techniques. Cultures were restimulated every 7-10 days using autologous primary fibroblasts retrovirally transduced with P501S. Following four stimulation cycles, CD8+ T cell lines were identified that specifically produced interferon-γ when stimulated with P501S-transduced autologous fibroblasts. The P501S-specific activity could be sustained by the continued stimulation of the cultures with P501S-transduced fibroblasts in the presence of IL-15. A panel of HLA-mismatched fibroblast lines transduced with P501S were generated to define the restriction allele of the response. By measuring interferon-γ in an ELISPOT assay, the P501S specific response was shown to be restricted by HLA-A2. These results demonstrate that a CD8+ CTL response to P501S can be elicited.

## EXAMPLE 10 IDENTIFICATION OF A NATURALLY PROCESSED CTL EPITOPE CONTAINED WITHIN A PROSTATE TUMOR ANTIGEN

The 9-mer peptide p5 (SEQ ID NO: 338) was derived from the P703P antigen (also referred to as P20). The p5 peptide is immunogenic in human HLA-A2 donors and is a naturally processed epitope. Antigen specific CD8+ T cells can be primed following repeated in vitro stimulations with monocytes pulsed with p5 peptide. These CTL specifically recognize p5-pulsed target cells in both ELISPOT (as described above) and chromium release assays. Additionally, immunization of HLA-A2 transgenic mice with p5 leads to the generation of CTL lines which recognize a variety of P703P transduced target cells expressing either HLA-A2Kb or HLA-A2. Specifically, HLA-A2 transgenic mice were immunized subcutaneously in the footpad with 100 µg of p5 peptide together with 140 µg of hepatitis B virus core peptide (a Th peptide) in Freund's incomplete adjuvant. Three weeks post immunization, spleen cells from immunized mice were stimulated in vitro with peptide-pulsed LPS blasts. CTL activity was assessed by chromium release assay five days after primary in vitro stimulation. Retrovirally transduced cells expressing the control antigen P703P and HLA-A2Kb were used as targets. CTL lines that specifically recognized both p5-pulsed targets as well as P703P-expressing targets were identified.

Human *in vitro* priming experiments demonstrated that the p5 peptide is immunogenic in humans. Dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by culturing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, the DC were pulsed with p5 peptide and cultured with GM-CSF and IL-4 together with CD8+ T cell enriched PBMC. CTL lines were restimulated on a weekly basis

with p5-pulsed monocytes. Five to six weeks after initiation of the CTL cultures, CTL recognition of p5-pulsed target cells was demonstrated.

## EXAMPLE 11 EXPRESSION OF A BREAST TUMOR-DERIVED ANTIGEN IN PROSTATE

Isolation of the antigen B305D from breast tumor by differential display is described in US Patent Application No. 08/700,014, filed August 20, 1996. Several different splice forms of this antigen were isolated. The determined cDNA sequences for these splice forms are provided in SEQ ID NO: 366-375, with the predicted amino acid sequences corresponding to the sequences of SEQ ID NO: 292, 298 and 301-303 being provided in SEQ ID NO: 299-306, respectively.

The expression levels of B305D in a variety of tumor and normal tissues were examined by real time PCR and by Northern analysis. The results indicated that B305D is highly expressed in breast tumor, prostate tumor, normal prostate tumor and normal testes, with expression being low or undetectable in all other tissues examined (colon tumor, lung tumor, ovary tumor, and normal bone marrow, colon, kidney, liver, lung, ovary, skin, small intestine, stomach).

## EXAMPLE 12 ELICITATION OF PROSTATE TUMOR ANTIGEN-SPECIFIC CTL RESPONSES IN HUMAN BLOOD

This Example illustrates the ability of a prostate tumor antigen to elicit a CTL response in blood of normal humans.

Autologous dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal donors by growth for five days in RPMI medium containing 10% human serum, 50 ng/ml GMCSF and 30 ng/ml IL-4. Following culture, DC were infected overnight with recombinant P501S-expressing vaccinia virus at an M.O.I. of 5 and matured for 8 hours by the addition of 2 micrograms/ml CD40 ligand. Virus was inactivated by UV irradiation, CD8+ cells were isolated by positive selection using magnetic beads, and priming cultures were initiated in 24-well plates. Following five stimulation cycles, CD8+ lines were identified that specifically produced interferon-gamma when stimulated with autologous P501S-transduced fibroblasts. The P501S-specific activity of cell line 3A-1 could be maintained following additional stimulation cycles on autologous B-LCL transduced with P501S. Line 3A-1 was shown to specifically recognize autologous B-LCL transduced to

express P501S, but not EGFP-transduced autologous B-LCL, as measured by cytotoxity assays (<sup>51</sup>Cr release) and interferon-gamma production (Interferon-gamma Elispot; *see* above and Lalvani et al., *J. Exp. Med. 186*:859-865, 1997). The results of these assays are presented in Figures 6A and 6B.

# EXAMPLE 13 IDENTIFICATION OF PROSTATE TUMOR ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of certain prostate tumor polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 372 clones were identified, and 319 were successfully sequenced. Table I presents a summary of these clones, which are shown in SEQ ID NOs:385-400. Of these sequences SEQ ID NOs:386, 389, 390 and 392 correspond to novel genes, and SEQ ID NOs: 393 and 396 correspond to previously identified sequences. The others (SEQ ID NOs:385, 387, 388, 391, 394, 395 and 397-400) correspond to known sequences, as shown in Table I.

69
Table I
Summary of Prostate Tumor Antigens

Known Genes	Previously identified Genes	Novel Genes
T-cell gamma chain	P504S	23379 (SEQ ID NO:389)
Kallikrein	P1000C	23399 (SEQ ID NO:392)
Vector	P501S	23320 (SEQ ID NO:386)
CGI-82 protein mRNA (23319; SEQ ID NO:385)	P503S	23381 (SEQ ID NO:390)
PSA	P510S	
Ald. 6 Dehyd,	P784P	
L-iditol-2 dehydrogenase (23376; SEQ ID NO:388)	P502S	
Ets transcription factor PDEF (22672; SEQ ID NO:398)	P706P	
hTGR (22678; SEQ ID NO:399)	19142.2, bangur.seq (22621; SEQ ID NO:396)	
KIAA0295(22685; SEQ ID NO:400)	5566.1 Wang(23404; SEQ ID NO:393)	
Prostatic Acid Phosphatase(22655; SEQ ID NO:397)	P712P	

transglutaminase (22611; SEQ ID NO:395)	P778P	
HDLBP (23508; SEQ ID NO:394)		
CGI-69 Protein(23367; SEQ ID NO:387)		
KIAA0122(23383; SEQ ID NO:391)		
TEEG		

CGI-82 showed 4.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 43% of prostate tumors, 25% normal prostate, not detected in other normal tissues tested. L-iditol-2 dehydrogenase showed 4.94 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 90% of prostate tumors, 100% of normal prostate, and not detected in other normal tissues tested. Ets transcription factor PDEF showed 5.55 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% prostate tumors, 25% normal prostate and not detected in other normal tissues tested. hTGR1 showed 9.11 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 63% of prostate tumors and is not detected in normal tissues tested including normal prostate. KIAA0295 showed 5.59 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% of prostate tumors, low to undetectable in normal tissues tested including normal prostate tissues. Prostatic acid phosphatase showed 9.14 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 67% of prostate tumors, 50% of normal prostate, and not detected in other normal tissues tested. Transglutaminase showed 14.84 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 30% of prostate tumors, 50% of normal prostate, and is not detected in other normal tissues tested. High density lipoprotein binding protein (HDLBP) showed 28.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% of normal prostate, and is undetectable in all other normal tissues tested. CGI-69 showed 3.56 fold over-expression in prostate tissues as compared to other normal tissues tested. It is a low abundant gene, detected in more than 90% of prostate tumors, and in 75% normal prostate tissues. The expression of this gene in normal tissues was very low. KIAA0122 showed 4.24 fold over-expression in prostate

71

tissues as compared to other normal tissues tested. It was over-expressed in 57% of prostate tumors, it was undetectable in all normal tissues tested including normal prostate tissues. 19142.2 bangur showed 23.25 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors and 100% of normal prostate. It was undetectable in other normal tissues tested. 5566.1 Wang showed 3.31 fold over-expression in prostate tissues as compared to other normal tissues tested. It was overexpressed in 97% of prostate tumors, 75% normal prostate and was also over-expressed in normal bone marrow, pancreas, and activated PBMC. Novel clone 23379 showed 4.86 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in 97% of prostate tumors and 75% normal prostate and is undetectable in all other normal tissues tested. Novel clone 23399 showed 4.09 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 27% of prostate tumors and was undetectable in all normal tissues tested including normal prostate tissues. Novel clone 23320 showed 3.15 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in all prostate tumors and 50% of normal prostate tissues. It was also expressed in normal colon and trachea. Other normal tissues do not express this gene at high level.

# EXAMPLE 14 IDENTIFICATION OF PROSTATE TUMOR ANTIGENS BY ELECTRONIC SUBTRACTION

This Example describes the use of an electronic subtraction technique to identify prostate tumor antigens.

Potential prostate-specific genes present in the GenBank human EST database were identified by electronic subtraction (similar to that described by Vasmatizis et al., *Proc. Natl. Acad. Sci. USA 95*:300-304, 1998). The sequences of EST clones (43,482) derived from various prostate libraries were obtained from the GenBank public human EST database. Each prostate EST sequence was used as a query sequence in a BLASTN (National Center for Biotechnology Information) search against the human EST database. All matches considered identical (length of matching sequence >100 base pairs, density of identical matches over this region > 70%) were grouped (aligned) together in a cluster. Clusters containing more than 200 ESTs were discarded since they probably represented repetitive elements or highly expressed genes such as those for ribosomal proteins. If two or more clusters shared common ESTs, those clusters were grouped together into a "supercluster," resulting in 4,345 prostate superclusters.

Records for the 479 human cDNA libraries represented in the GenBank release were downloaded to create a database of these cDNA library records. These 479 cDNA libraries were grouped into three groups, Plus (normal prostate and prostate tumor libraries, and breast cell lines, in which expression was desired), Minus (libraries from other normal adult tissues, in which expression was not desirable), and Other (fetal tissue, infant tissue, tissues found only in women, non-prostate tumors and cell lines other than prostate cell lines, in which expression was considered to be irrelevant). A summary of these library groups is presented in Table II.

<u>Table II</u>
Prostate cDNA Libraries and ESTs

Frostate cDNA Libraries and ESTs				
# of Libraries	# of ESTs			
25	43,482			
11	18,875			
11	21,769			
3	2,838			
166				
287				
	# of Libraries  25  11  11  3  166			

Each supercluster was analyzed in terms of the ESTs within the supercluster. The tissue source of each EST clone was noted and used to classify the superclusters into four groups: Type 1- EST clones found in the Plus group libraries only; no expression detected in Minus or Other group libraries; Type 2- EST clones found in the Plus and Other group libraries only; no expression detected in the Minus group; Type 3- EST clones found in the Plus, Minus and Other group libraries, but the expression in the Plus group is higher than in either the Minus or Other groups; and Type 4- EST clones found in Plus, Minus and Other group libraries, but the expression in the Plus group is higher than the expression in the Minus group. This analysis identified 4,345 breast clusters (see Table III). From these clusters, 3,172 EST clones were ordered from Research Genetics, Inc., and were received as frozen glycerol stocks in 96-well plates.

<u>Table III</u> <u>Prostate Cluster Summary</u>

Туре	# of Superclusters	# of ESTs Ordered
1	688	677
2	2899	2484
3	. 85	11
4	673	0
Total	4345	3172

The inserts were PCR-amplified using amino-linked PCR primers for Synteni microarray analysis. When more than one PCR product was obtained for a particular clone, that PCR product was not used for expression analysis. In total, 2,528 clones from the electronic subtraction method were analyzed by microarray analysis to identify electronic subtraction breast clones that had high tumor vs. normal tissue mRNA. Such screens were performed using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Within these analyses, the clones were arrayed on the chip, which was then probed with fluorescent probes generated from normal and tumor prostate cDNA, as well as various other normal tissues. The slides were scanned and the fluorescence intensity was measured.

Clones with an expression ratio greater than 3 (i.e., the level in prostate tumor cDNA was at least three times the level in normal prostate cDNA) were identified as prostate tumor-specific sequences (Table IV). The sequences of these clones are provided in SEQ ID NOs:401-453, with certain novel sequences shown in SEQ ID NOs:407, 413, 416-419, 422, 426, 427 and 450.

<u>Table IV</u> <u>Prostate-tumor Specific Clones</u>

SEQ ID NO.	Sequence Designation	Comments
401	22545	previously identified P1000C
402	22547	previously identified P704P

WO 00/04149 PCT/US99/15838 ··

403	22548	known
404	22550	known
405	22551	PSA
406	22552	prostate secretory protein 94
407	22553	novel
408	22558	previously identified P509S
409	22562	glandular kallikrein
410	22565	previously identified P1000C
411	22567	PAP
412	22568	B1006C (breast tumor antigen)
413	22570	novel
414	22571	PSA
415	22572	previously identified P706P
416	22573	novel
417	22574	novel
418	22575	novel
419	22580	novel
420	22581	PAP
421	22582	prostatic secretory protein 94
422	22583	novel
423	22584	prostatic secretory protein 94
424	22585	prostatic secretory protein 94
425	22586	known
426	22587	novel
427	22588	novel
428	22589	PAP
429	22590	known
430	22591	PSA
431	22592	known
432	22593	Previously identified P777P
433	22594	T cell receptor gamma chain
434	22595	Previously identified P705P
435	22596	Previously identified P707P
436	22847	PAP
437	22848	known
438	22849	prostatic secretory protein 57

	<del></del>	T
439	22851	PAP
440	22852	PAP
441	22853	PAP
442	22854	previously identified P509S
443	22855	previously identified P705P
444	22856	previously identified P774P
445	22857	PSA
446	23601	previously identified P777P
447	23602	PSA
448	23605	PSA
449	23606	PSA
450	23612	novel
451	23614	PSA
452	23618	previously identified P1000C
453	23622	previously identified P705P

## EXAMPLE 15 FURTHER IDENTIFICATION OF PROSTATE TUMOR ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of additional prostate tumor polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 142 clones were identified and sequenced. Certain of these clones are shown in SEQ ID NOs:454-467. Of these sequences SEQ ID NOs:459-461 correspond to novel genes. The others (SEQ ID NOs:454-458 and 461-467) correspond to known sequences.

### EXAMPLE 16 FURTHER CHARACTERIZATION OF PROSTATE TUMOR ANTIGEN P710P

This Example describes the full length cloning of P710P.

76

The prostate cDNA library described above was screened with the P710P fragment described above. One million colonies were plated on LB/Ampicillin plates. Nylon membrane filters were used to lift these colonies, and the cDNAs picked up by these filters were then denatured and cross-linked to the filters by UV light. The P710P fragment was radiolabeled and used to hybridize with the filters. Positive cDNA clones were selected and their cDNAs recovered and sequenced by an automatic ABI Sequencer. Four sequences were obtained, and are presented in SEQ ID NOs:468-471.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the present invention is not limited except as by the appended claims.

### **CLAIMS**

- 1. An isolated polypeptide comprising at least an immunogenic portion of a prostate tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (a) sequences recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472;
- (b) sequences that hybridize to any of the foregoing sequences under moderately stringent conditions; and
  - (c) complements of any of the sequence of (a) or (b).
- 2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing polynucleotide sequences.
- 3. An isolated polypeptide comprising a sequence recited in any one of SEQ ID NO: 108, 112, 113, 114, 172, 176, 178, 327, 329, 331, 339 and 383.
- 4. An isolated polynucleotide encoding at least 15 amino acid residues of a prostate tumor protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434,

435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing sequences.

78

- 5. An isolated polynucleotide encoding a prostate tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing sequences.
- 6. An isolated polynucleotide comprising a sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472.
- 7. An isolated polynucleotide comprising a sequence that hybridizes, under moderately stringent conditions, to a sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472.
- 8. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 4-7.
- 9. An expression vector comprising a polynucleotide according to any one of claims 4-7.
- A host cell transformed or transfected with an expression vector according to claim 9.
  - 11. An expression vector comprising a polynucleotide according claim 8.

- 12. A host cell transformed or transfected with an expression vector according to claim 11.
- 13. A pharmaceutical composition comprising a polypeptide according to claim 1, in combination with a physiologically acceptable carrier.
- 14. A vaccine comprising a polypeptide according to claim 1, in combination with a non-specific immune response enhancer.
- 15. A vaccine according to claim 14, wherein the non-specific immune response enhancer is an adjuvant.
- 16. A vaccine according to claim 14, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 17. A pharmaceutical composition comprising a polynucleotide according to claim 4, in combination with a physiologically acceptable carrier.
- 18. A vaccine comprising a polynucleotide according to claim 4, in combination with a non-specific immune response enhancer.
- 19. A vaccine according to claim 18, wherein the non-specific immune response enhancer is an adjuvant.
- 20. A vaccine according to claim 18, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 21. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a prostate tumor protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472 or a complement of any of the foregoing polynucleotide sequences.

- 22. A pharmaceutical composition comprising an antibody or fragment thereof according to claim 18, in combination with a physiologically acceptable carrier.
- 23. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.
- 24. A pharmaceutical composition according to claim 23, wherein the antigen presenting cell is a dendritic cell or a macrophage.
- 25. A vaccine comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a non-specific immune response enhancer.
- 26. A vaccine according to claim 25, wherein the non-specific immune response enhancer is an adjuvant.
- 27. A vaccine according to claim 25, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 28. A vaccine according to claim 25, wherein the antigen-presenting cell is a dendritic cell.
- 29. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a polypeptide according to claim 1, and thereby inhibiting the development of a cancer in the patient.
- 30. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a polynucleotide according to claim 4, and thereby inhibiting the development of a cancer in the patient.
- 31. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antibody or antigen-binding fragment thereof according to claim 21, and thereby inhibiting the development of a cancer in the patient.

- 32. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide according to claim 1, and thereby inhibiting the development of a cancer in the patient.
- 33. A method according to claim 32, wherein the antigen-presenting cell is a dendritic cell.
- 34. A method according to any one of claims 29-32, wherein the cancer is prostate cancer.
- 35. A fusion protein comprising at least one polypeptide according to claim 1.
- 36. A fusion protein according to claim 35, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.
- 37. A fusion protein according to claim 35, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.
- 38. A fusion protein according to claim 35, wherein the fusion protein comprises an affinity tag.
- 39. An isolated polynucleotide encoding a fusion protein according to claim 35.
- 40. A pharmaceutical composition comprising a fusion protein according to claim 32, in combination with a physiologically acceptable carrier.
- 41. A vaccine comprising a fusion protein according to claim 35, in combination with a non-specific immune response enhancer.
- 42. A vaccine according to claim 41, wherein the non-specific immune response enhancer is an adjuvant.

43. A vaccine according to claim 41, wherein the non-specific immune response enhancer induces a predominantly Type I response.

- 44. A pharmaceutical composition comprising a polynucleotide according to claim 40, in combination with a physiologically acceptable carrier.
- 45. A vaccine comprising a polynucleotide according to claim 40, in combination with a non-specific immune response enhancer.
- 46. A vaccine according to claim 45, wherein the non-specific immune response enhancer is an adjuvant.
- 47. A vaccine according to claim 45, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 48. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 40 or claim 44.
- 49. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a vaccine according to claim 41 or claim 45.
- 50. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (i) polynucleotides recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472; and
  - (ii) complements of the foregoing polynucleotides;

wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the prostate tumor protein from the sample.

51. A method according to claim 50, wherein the biological sample is blood or a fraction thereof.

- 52. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 50.
- 53. A method for stimulating and/or expanding T cells specific for a prostate tumor protein, comprising contacting T cells with one or more of:
  - (i) a polypeptide according to claim 1;
- (ii) a polypeptide encoded by a polynucleotide comprising a sequence provided in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472;
  - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); and/or
- (iv) an antigen presenting cell that expresses a polypeptide of (i) or (ii); under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.
- 54. An isolated T cell population, comprising T cells prepared according to the method of claim 53.
- 55. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population according to claim 54.
- 56. A method for inhibiting the development of a cancer in a patient, comprising the steps of:
- (a) incubating CD4<sup>+</sup> and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:
  - (i) a polypeptide according to claim 1;
- (ii) a polypeptide encoded by a polynucleotide comprising a sequence of any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472;
  - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); or
- (iv) an antigen-presenting cell that expresses a polypeptide of (i) or (ii);

such that T cells proliferate; and

(b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.

(ii);

- 57. A method for inhibiting the development of a cancer in a patient, comprising the steps of:
- (a) incubating CD4<sup>+</sup> and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:
  - (i) a polypeptide according to claim 1;
- (ii) a polypeptide encoded by a polynucleotide comprising a sequence of any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472;
  - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); or
  - (iv) an antigen-presenting cell that expresses a polypeptide of (i) or

such that T cells proliferate;

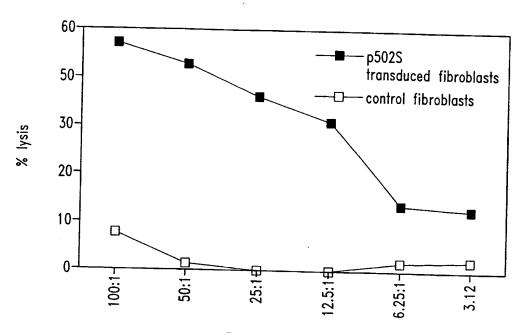
- (b) cloning at least one proliferated cell; and
- (c) administering to the patient an effective amount of the cloned T cells, and thereby inhibiting the development of a cancer in the patient.
- 58. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with a binding agent that binds to a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (i) polynucleotides recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472; and
  - (ii) complements of the foregoing polynucleotides;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.
- 59. A method according to claim 58, wherein the binding agent is an antibody.
- 60. A method according to claim 59, wherein the antibody is a monoclonal antibody.

- 61. A method according to claim 58, wherein the cancer is prostate cancer.
- 62. A method for monitoring the progression of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472, or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent;
- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and
- (d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
- 63. A method according to claim 62, wherein the binding agent is an antibody.
- 64. A method according to claim 63, wherein the antibody is a monoclonal antibody.
- 65. A method according to claim 62, wherein the cancer is a prostate cancer.
- 66. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472, or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and

- (c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.
- 67. A method according to claim 66, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.
- 68. A method according to claim 66, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.
- 69. A method for monitoring the progression of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472, or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide;
- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and
- (d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
- 70. A method according to claim 69, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.
- 71. A method according to claim 69, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.
  - 72. A diagnostic kit, comprising:
  - (a) one or more antibodies according to claim 21; and
  - (b) a detection reagent comprising a reporter group.

WO 00/04149 PCT/US99/15838 · ·

- 73. A kit according to claim 72, wherein the antibodies are immobilized on a solid support.
- 74. A kit according to claim 73, wherein the solid support comprises nitrocellulose, latex or a plastic material.
- 75. A kit according to claim 72, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.
- 76. A kit according to claim 72, wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.
- 77. An oligonucleotide comprising 10 to 40 nucleotides that hybridize under moderately stringent conditions to a polynucleotide that encodes a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing polynucleotides.
- 78. A oligonucleotide according to claim 77, wherein the oligonucleotide comprises 10-40 nucleotides recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472.
  - 79. A diagnostic kit, comprising:
  - (a) an oligonucleotide according to claim 77; and
- (b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.



Effector: Target Ratio

Fig. 1

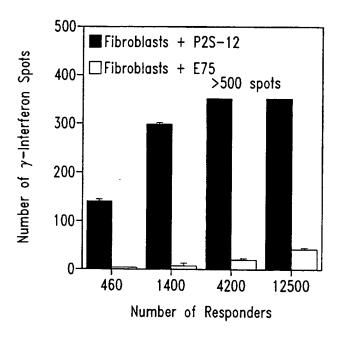


Fig. 2A

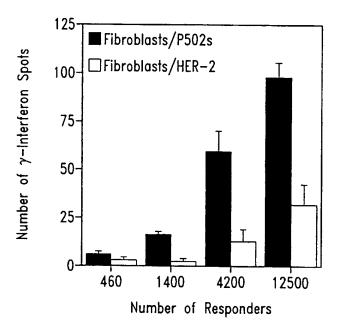
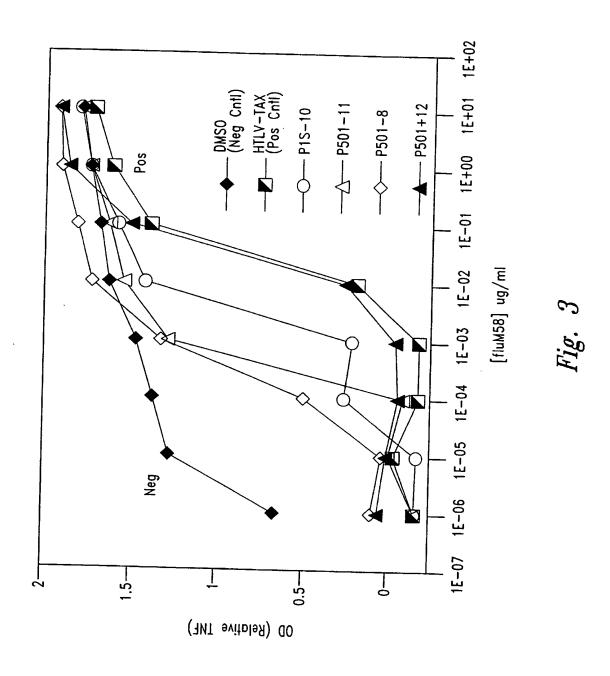


Fig. 2B

SUBSTITUTE SHEET (RULE 26)



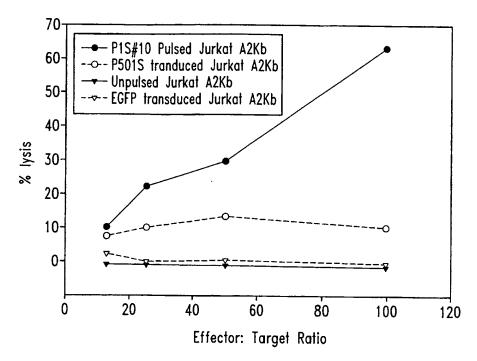
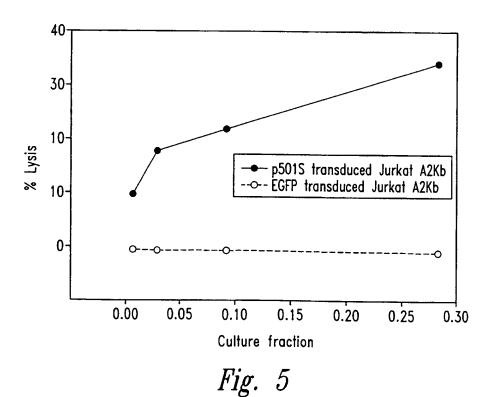
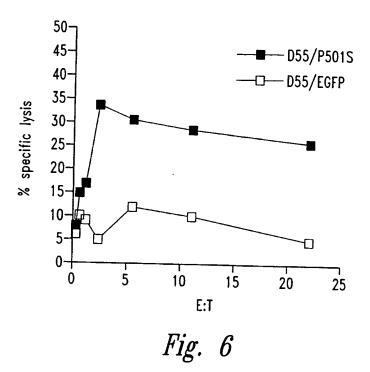
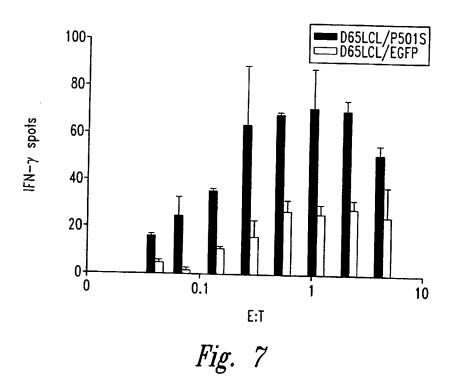


Fig. 4



SUBSTITUTE SHEET (RULE 26)





SUBSTITUTE SHEET (RULE 26)

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#### SEQUENCE LISTING

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 tegeteattg atcetngene eeggtetteg getgeggnga aeggtteact ceteaaagge
                                                                        720
                                                                        780
 ggtntnccgg ttatccccaa acnggggata cccnga
                                                                        816
       <210> 3
       <211> 773
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(773)
       <223> n = A,T,C or G
       <400> 3
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 teetgeteet cactggtgat aaacgageee egtteettgt tgtgateatg atgaacaace
tcctcaaaag tcagaaccgg agtcacacag gcatctgtgc cgtcaaagat ttgacaccac
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tctgccttcg tcttctttgc aaatacatct gcaaacttct tcttcatttc tggccaatca
                                                                        180
tccatgctca tctgattggg aagttcatca gactttagtc canntccttt gatcagcagc
                                                                        240
togtagaact ggggttctat tgctccaaca gccatgaatt ccccatctgc tgtcctgtaa
                                                                        300
gtcgtataga aaggtgctcc accatccaac atgttctgtc ctcgaggggg ggcccggtac
                                                                       360
ccaattegee ctatantgag tegtattaeg egegeteact ggeegtegtt ttacaaegte
                                                                       420
gtgactggga aaaccctggg cgttaccaac ttaatcgcct tgcagcacat ccccctttcg
                                                                       480
ccagctgggc gtaatancga aaaggcccgc accgatcgcc cttccaacag ttgcgcacct
                                                                       540
gaatgggnaa atgggacccc cctgttaccg cgcattnaac ccccgcnggg tttngttgtt
                                                                       600
acceccaent nnacegetta caetttgeca gegeettane gecegeteee ttteneettt
                                                                       660
ettecettee ttteneneen ettteeeceg gggttteeec enteaaacee ena
                                                                       720
                                                                       773
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      <211> 828
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(828)
      <223> n = A,T,C or G
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aatgggcaga cacaggtgta tgccaatgtt tctgaaatgg gtataatttc gtcctcct
                                                                        60
                                                                       120
toggaacact ggctgtctct gaagacttct cgctcagttt cagtgaggac acacacaaag
acgtgggtga ccatgttgtt tgtggggtgc agagatggga ggggtggggc ccaccctgga
                                                                       180
agagtggaca gtgacacaag gtggacactc tctacagatc actgaggata agctggagcc
                                                                       240
                                                                      300
acaatgcatg aggcacacac acagcaagga tgacnctgta aacatagccc acgctgtcct
                                                                      360
```

```
gngggcactg ggaagcctan atnaggccgt gagcanaaag aaggggagga tccactaqtt
                                                                       420
ctanagcggc cgccaccgcg gtgganctcc ancttttgtt ccctttagtg agggttaatt
                                                                       480
gcgcgcttgg cntaatcatg gtcatanctn tttcctgtgt gaaattgtta tccgctcaca
                                                                       540
attccacaca acatacganc cggaaacata aantgtaaac ctggggtgcc taatgantga
                                                                       600
ctaactcaca ttaattgcgt tgcgctcact gcccgctttc caatcnggaa acctgtcttg
                                                                       660
concttgcat tnatgaaton gocaaccccc ggggaaaagc gtttgcgttt tgggcgctct
                                                                       720
teegetteet eneteantta nteectnene teggteatte eggetgenge aaaceggtte
                                                                       780
accncctcca aagggggtat tccggtttcc ccnaatccgg gganancc
                                                                       828
      <210> 5
      <211> 834
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(834)
      <223> n = A,T,C or G
      <400> 5
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agttttaatt gcatccaaag tactaacaaa aactctagca atcaagaatg gcagcatgtt
                                                                      120
attttataac aatcaacacc tgtggctttt aaaatttggt tttcataaga taatttatac
                                                                      180
tgaagtaaat ctagccatgc ttttaaaaaa tgctttaggt cactccaagc ttggcagtta
                                                                      240
acatttggca taaacaataa taaaacaatc acaatttaat aaataacaaa tacaacattg
                                                                      300
taggccataa tcatatacag tataaggaaa aggtggtagt gttgagtaag cagttattag
                                                                      360
aatagaatac cttggcctct atgcaaatat gtctagacac tttgattcac tcagcctga
                                                                      420
cattcagttt tcaaagtagg agacaggttc tacagtatca ttttacagtt tccaacacat
                                                                      480
tgaaaacaag tagaaaatga tgagttgatt tttattaatg cattacatcc tcaagagtta
                                                                      540
tcaccaaccc ctcagttata aaaaattttc aagttatatt agtcatataa cttggtgtgc
                                                                      600
ttattttaaa ttagtgctaa atggattaag tgaagacaac aatggtcccc taatgtgatt
                                                                      660
gatattggtc atttttacca gcttctaaat ctnaactttc aggcttttga actggaacat
                                                                      720
tgnatnacag tgttccanag ttncaaccta ctggaacatt acagtgtgct tgattcaaaa
                                                                      780
tgttattttg ttaaaaaatta aattttaacc tggtggaaaa ataatttgaa atna
                                                                      834
      <210> 6
      <211> 818
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(818)
      <223> n = A,T,C or G
      <400> 6
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                                                                       60
aaccacatct acaaaatgcc agtatcaggc ggcggcttcg aagccaaagt gatgtttgga
                                                                      120
tgtaaagtga aatattagtt ggcggatgaa gcagatagtg aggaaagttg agccaataat
                                                                      180
gacgtgaagt ccgtggaagc ctgtggctac aaaaaatgtt gagccgtaga tgccgtcgga
                                                                      240
aatggtgaag ggagactcga agtactctga ggcttgtagg agggtaaaat agagacccag
                                                                      300
taaaattgta ataagcagtg cttgaattat ttggtttcgg ttgttttcta ttagactatg
                                                                      360
gtgagctcag gtgattgata ctcctgatgc gagtaatacg gatgtgttta ggagtgggac
                                                                      420
ttctagggga tttagcgggg tgatgcctgt tgggggccag tgccctccta gttggggggt
                                                                      480
aggggctagg ctggagtggt aaaaggctca gaaaaatcct gcgaagaaaa aaacttctga
                                                                      540
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```
ggtaataaat aggattatcc cgtatcgaag gcctttttgg acaggtggtg tgtggtggcc
                                                                        600
 ttggtatgtg ctttctcgtg ttacatcgcg ccatcattgg tatatggtta gtgtgttggg
                                                                        660
 ttantanggc ctantatgaa gaacttttgg antggaatta aatcaatngc ttggccggaa
                                                                        720
 gtcattanga nggctnaaaa ggccctgtta ngggtctggg ctnggtttta cccnacccat
                                                                        780
 ggaatnence ecceggaena ntgnatecet attettaa
                                                                        818
       <210> 7
       <211> 817
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(817)
       <223> n = A,T,C or G
       <400> 7
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cgggccctat ttcaaagatt tttaggggaa ttaattctag gacgatgggt atgaaactgt
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ggtttgctcc acagatttca gagcattgac cgtagtatac ccccggtcgt gtagcggtga
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aagtggtttg gtttagacgt ccgggaattg catctgtttt taagcctaat gtggggacag
                                                                        240
ctcatgagtg caagacgtct tgtgatgtaa ttattatacn aatgggggct tcaatcggga
                                                                        300
gtactactcg attgtcaacg tcaaggagtc gcaggtcgcc tggttctagg aataatgggg
                                                                        360
gaagtatgta ggaattgaag attaatccgc cgtagtcggt gttctcctag gttcaatacc
                                                                        420
attggtggcc aattgatttg atggtaaggg gagggatcgt tgaactcgtc tgttatgtaa
aggatneett ngggatggga aggenatnaa ggaetangga tnaatggegg geangatatt
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tcaaacngtc tctanttcct gaaacgtctg aaatgttaat aanaattaan tttngttatt
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                                                                       600
gaatnttnng gaaaagggct tacaggacta gaaaccaaat angaaaanta atnntaangg
                                                                       660
enttatentn aaaggtnata aceneteeta tnateeeace caatngnatt eeceaenenn
                                                                       720
acnattggat nececantte canaaangge enceceegg tgnanneene ettttgttee
                                                                       780
cttnantgan ggttattcnc ccctngcntt atcancc
                                                                       817
      <210> 8
      <211> 799
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(799)
      <223> n = A, T, C \text{ or } G
      <400> 8
cattlccggg tttactttct aaggaaagcc gagcggaagc tgctaacgtg ggaatcggtg
                                                                        60
cataaggaga actttctgct ggcacgcgct agggacaagc gggagagcga ctccgagcgt
                                                                       120
ctgaagcgca cgtcccagaa ggtggacttg gcactgaaac agctgggaca catccgcgag
                                                                       180
tacgaacagc gcctgaaagt gctggagcgg gaggtccagc agtgtagccg cgtcctgggg
                                                                       240
tgggtggccg angcctganc cgctctgcct tgctgcccc angtgggccg ccacccctg
                                                                       300
acctgcctgg gtccaaacac tgagccctgc tggcggactt caagganaac ccccacangg
                                                                       360
ggattttgct cctanantaa ggctcatctg ggcctcggcc ccccacctg gttggccttg
                                                                       420
tetttgangt gagececatg tecatetggg ceaetgteng gaccacettt ngggagtgtt
ctccttacaa ccacannatg cccggctcct cccggaaacc antcccancc tgngaaggat
                                                                       480
caagneetgn atceactnnt netanaaceg geenceneeg engtggaace encettntgt
                                                                       540
tcettttent tnagggttaa tnnegeettg geettneean ngteetnene ntttteennt
                                                                      600
                                                                       660
gttnaaattg ttangcnccc nccnntcccn cnncnncnan cccgacccnn annttnnann
                                                                       720
```

```
ncctgggggt nccnncngat tgacconncc nccctntant tgcnttnggg nncnntgccc
                                                                        780
ctttccctct nggganncg
                                                                        799
      <210> 9
      <211> 801
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(801)
      <223> n = A,T,C or G
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taangatgac actcccaaag gtggtcctga cagtggccca gatggacatg gggctcacct
                                                                        120
caaggacaag gccaccaggt gcgggggccg aagcccacat gatccttact ctatgagcaa
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aatcccctgt gggggcttct ccttgaagtc cgccancagg gctcagtctt tggacccang
                                                                        240
caggicatgg ggitgingne caactggggg ceneaacgea aaanggenea gggeetengn
                                                                        300
cacccatccc angacgeggc tacactnetg gacetecene tecaccaett teatgegetg
                                                                        360
ttentacceg egnatntgte ceanctgttt engtgeenac tecancttet nggaegtgeg
                                                                        420
ctacatacgc ccggantene neteccgett tgtecetate cacgtnecan caacaaattt
                                                                        480
cncentantg cacenattee caenttinne agnitteene nnegngette etintaaaag
                                                                        540
ggttganccc cggaaaatnc cccaaagggg gggggccngg tacccaactn ccccctnata
                                                                       600
gctgaantcc ccatnaccnn gnctcnatgg ancentcent tttaannacn ttctnaactt
                                                                       660
gggaanance etegneentn ecceenttaa teeeneettg enangnnent ecceenntee
                                                                       720
ncccnnntng gentntnann cnaaaaagge cennnancaa teteetnnen eeteantteg
                                                                       780
ccanccctcg aaatcggccn c
                                                                       801
      <210> 10
      <211> 789
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(789)
      \langle 223 \rangle n = A,T,C or G
      <400> 10
cagtctatnt ggccagtgtg gcagctttcc ctgtggctgc cggtgccaca tgcctgtccc
                                                                        60
acagtgtggc cgtggtgaca gcttcagccg ccctcaccgg gttcaccttc tcagccctgc
                                                                       120
agatectgee ctacacactg geeteeetet accaceggga gaageaggtg tteetgeeca
                                                                       180
aataccgagg ggacactgga ggtgctagca gtgaggacag cctgatgacc agcttcctgc
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caggccctaa gcctggagct cccttcccta atggacacgt gggtgctgga ggcagtggcc
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tgctcccacc tccacccgcg ctctgcgggg cctctgcctg tgatgtctcc gtacgtgtgg
                                                                       360
tggtgggtga gcccaccgan gccagggtgg ttccgggccg gggcatctgc ctggacctcg
                                                                       420
ccatcctgga tagtgcttcc tgctgtccca ngtggcccca tccctgttta tgggctccat
                                                                       480
tgtccagctc agccagtctg tcactgccta tatggtgtct gccgcaggcc tgggtctggt
                                                                       540
cccatttact ttgctacaca ggtantattt gacaagaacg anttggccaa atactcagcg
                                                                       600
ttaaaaaaatt ccagcaacat tgggggtgga aggcctgcct cactgggtcc aactccccqc
                                                                       660
tcctgttaac cccatggggc tgccggcttg gccgccaatt tctgttgctg ccaaantnat
                                                                       720
gtggctctct gctgccacct gttgctggct gaagtgcnta cngcncanct nggggggtng
                                                                       780
ggngttccc
                                                                       789
```

```
<210> 11
       <211> 772
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(772)
       <223> n = A,T,C or G
       <400> 11
 cccaccctac ccaaatatta gacaccaaca cagaaaagct agcaatggat tcccttctac
                                                                         60
 tttgttaaat aaataagtta aatatttaaa tgcctgtgtc tctgtgatgg caacagaagg
 accaacaggc cacatcctga taaaaggtaa gaggggggtg gatcagcaaa aagacagtgc
                                                                        120
                                                                        180
tgtgggctga ggggacctgg ttcttgtgtg ttgcccctca ggactcttcc cctacaaata
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actiticatat gitcaaatcc catggaggag tgittcatcc tagaaactcc catgcaagag
                                                                        300
ctacattaaa cgaagctgca ggttaagggg cttanagatg ggaaaccagg tgactgagtt
tattcagctc ccaaaaaccc ttctctaggt gtgtctcaac taggaggcta gctgttaacc
                                                                        360
ctgagcctgg gtaatccacc tgcagagtcc ccgcattcca gtgcatggaa cccttctggc
                                                                        420
ctccctgtat aagtccagac tgaaaccccc ttggaaggnc tccagtcagg cagccctana
                                                                        480
aactggggaa aaaagaaaag gacgccccan cccccagctg tgcanctacg cacctcaaca
                                                                        540
                                                                        600
gcacagggtg gcagcaaaaa aaccacttta ctttggcaca aacaaaaact ngggggggca
                                                                        660
acccggcac cccnangggg gttaacagga ancngggnaa cntggaaccc aattnaggca
                                                                        720
ggcccnccac cccnaatntt gctgggaaat ttttcctccc ctaaattntt tc
                                                                        772
      <210> 12
      <211> 751
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(751)
      \langle 223 \rangle n = A,T,C or G
      <400> 12
gccccaattc cagctgccac accacccacg gtgactgcat tagttcggat gtcatacaaa
                                                                        60
agctgattga agcaaccctc tactttttgg tcgtgagcct tttgcttggt gcaggtttca
                                                                       120
ttggctgtgt tggtgacgtt gtcattgcaa cagaatgggg gaaaggcact gttctctttg
                                                                       180
aagtanggtg agtcctcaaa atccgtatag ttggtgaagc cacagcactt gagccctttc
                                                                       240
atggtggtgt tccacacttg agtgaagtct tcctgggaac cataatcttt cttgatggca
                                                                       300
ggcactacca gcaacgtcag ggaagtgctc agccattgtg gtgtacacca aggcgaccac
agcagctgcn acctcagcaa tgaagatgan gaggangatg aagaagaacg tcncgagggc
                                                                       360
acacttgctc tcagtcttan caccatanca gcccntgaaa accaananca aagaccacna
                                                                       420
                                                                       480
cnccggctgc gatgaagaaa tnaccccncg ttgacaaact tgcatggcac tggganccac
agtggcccna aaaatcttca aaaaggatgc cccatcnatt gaccccccaa atgcccactg
                                                                       540
                                                                       600
ccaacagggg ctgccccacn cncnnaacga tganccnatt gnacaagatc tncntggtct
                                                                       660
tnatnaacnt gaaccctgcn tngtggctcc tgttcaggnc cnnggcctga cttctnaann
                                                                       720
aangaacten gaagneeeca enggananne g
                                                                       751
      <210> 13
      <211> 729
      <212> DNA
     <213> Homo sapien
```

```
<220>
      <221> misc_feature
      <222> (1)...(729)
      \langle 223 \rangle n = A,T,C or G
      <400> 13
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                                                                         60
tgtggancct cagcagtncc ctctttcaga actcantgcc aaganccctg aacaggagcc
                                                                        120
accatgcagt gcttcagctt cattaagacc atgatgatcc tcttcaattt gctcatcttt
                                                                        180
ctgtgtggtg cagccctgtt ggcagtgggc atctgggtgt caatcgatgg ggcatccttt
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ctgaagatct tcgggccact gtcgtccagt gccatgcagt ttgtcaacgt gggctacttc
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ctcatcgcag ccggcgttgt ggtcttagct ctaggtttcc tgggctgcta tggtgctaag
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actgagagca agtgtgccct cgtgacgttc ttcttcatcc tcctcctcat cttcattgct
                                                                        420
gaggttgcaa tgctgtggtc gccttggtgt acaccacaat ggctgagcac ttcctgacgt
                                                                        480
tgctggtaat gcctgccatc aanaaaagat tatgggttcc caggaanact tcactcaagt
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gttggaacac caccatgaaa gggctcaagt gctgtggctt cnnccaacta tacggattt
                                                                        600
qaagantcac ctacttcaaa gaaaanagtg cctttccccc atttctgttg caattgacaa
                                                                        660
acgtccccaa cacagccaat tgaaaacctg cacccaaccc aaangggtcc ccaaccanaa
                                                                        720
attnaaggg
                                                                        729
      <210> 14
      <211> 816
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(816)
      \langle 223 \rangle n = A,T,C or G
      <400> 14
tgctcttcct caaagttgtt cttgttgcca taacaaccac cataggtaaa gcgggcgcag
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tgttcgctga aggggttgta gtaccagcgc gggatgctct ccttgcagag tcctgtgtct
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ggcaggtcca cgcagtgccc tttgtcactg gggaaatgga tgcgctggag ctcgtcaaag
                                                                        180
ccactcgtgt atttttcaca ggcagcctcg tccgacgcgt cggggcagtt gggggtgtct
                                                                        240
tcacactcca ggaaactgtc natgcagcag ccattgctgc agcggaactg ggtgggctga
                                                                        300
cangigceag ageacactgg atggegeett tecatgnnan gggeeetgng ggaaagteee
                                                                        360
tganccccan anctgcctct caaangcccc accttgcaca ccccgacagg ctagaatgga
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atcttcttcc cgaaaggtag ttnttcttgt tgcccaancc ancccentaa acaaactctt
                                                                        480
gcanatctgc tccgnggggg tcntantacc ancgtgggaa aagaacccca ggcngcgaac
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caancttgtt tggatncgaa gcnataatct nctnttctgc ttggtggaca gcaccantna
                                                                        600
etgtnnanct ttagneentg gteetentgg gttgnnettg aacetaaten cennteaact
                                                                        660
gggacaaggt aantngccnt cctttnaatt cccnancntn ccccctggtt tggggttttn
                                                                        720
cncnctccta ccccagaaan nccgtgttcc cccccaacta ggggccnaaa ccnnttnttc
                                                                        780
cacaaccctn ccccacccac gggttcngnt ggttng
                                                                        816
      <210> 15
      <211> 783
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(783)
      <223> n = A, T, C \text{ or } G
```

60

```
<400> 15
  ccaaggcctg ggcaggcata nacttgaagg tacaacccca ggaacccctg gtgctgaagg
 atgtggaaaa cacagattgg cgcctactgc ggggtgacac ggatgtcagg gtagagagga
                                                                          60
 aagacccaaa ccaggtggaa ctgtggggac tcaaggaang cacctacctg ttccagctga
                                                                         120
 cagtgactag ctcagaccac ccagaggaca cggccaacgt cacagtcact gtgctgtcca
                                                                         180
 ccaagcagac agaagactac tgcctcgcat ccaacaangt gggtcgctgc cggggctctt
                                                                         240
 tcccacgctg gtactatgac cccacggagc agatctgcaa gagtttcgtt tatggaggct
                                                                         300
 gcttgggcaa caagaacaac taccttcggg aagaagagtg cattctancc tgtcngggtg
                                                                         360
 tgcaaggtgg gcctttgana ngcanctctg gggctcangc gactttcccc cagggcccct
                                                                         420
 ccatggaaag gcgccatcca ntgttctctg gcacctgtca gcccacccag ttccgctgca
                                                                         480
 ncaatggctg ctgcatcnac antttectng aattgtgaca acacceccca ntgcccccaa
                                                                         540
 ccctcccaac aaagcttccc tgttnaaaaa tacnccantt ggcttttnac aaacncccgg
                                                                         600
 cncctccntt ttccccnntn aacaaagggc nctngcnttt gaactgcccn aacccnggaa
                                                                         660
 tetneenngg aaaaantnee eeceetggtt eetnnaance eeteenenaa anetneeece
                                                                         720
                                                                         780
 CCC
                                                                         783
       <210> 16
       <211> 801
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(801)
       \langle 223 \rangle n = A,T,C or G
       <400> 16
gccccaattc cagctgccac accacccacg gtgactgcat tagttcggat gtcatacaaa
agctgattga agcaaccctc tactttttgg tcgtgagcct tttgcttggt gcaggtttca
                                                                         60
ttggctgtgt tggtgacgtt gtcattgcaa cagaatgggg gaaaggcact gttctctttg
                                                                        120
aagtagggtg agtcctcaaa atccgtatag ttggtgaagc cacagcactt gagccctttc
                                                                        180
atggtggtgt tccacacttg agtgaagtct tcctgggaac cataatcttt cttgatggca
                                                                        240
ggcactacca gcaacgtcag gaagtgctca gccattgtgg tgtacaccaa ggcgaccaca
                                                                        300
gcagctgcaa cctcagcaat gaagatgagg aggaggatga agaagaacgt cncgagggca
                                                                        360
cacttgctct ccgtcttagc accatagcag cccangaaac caagagcaaa gaccacaacg
                                                                        420
congotgoga atgaaagaaa ntacccacgt tgacaaactg catggccact ggacgacagt
                                                                        480
tggcccgaan atcttcagaa aagggatgcc ccatcgattg aacacccana tgcccactgc
                                                                        540
cnacagggct geneencnen gaaagaatga gecattgaag aaggatente ntggtettaa
                                                                        600
tgaactgaaa ccntgcatgg tggcccctgt tcagggctct tggcagtgaa ttctganaaa
                                                                        660
aaggaacngc ntnagccccc ccaaangana aaacaccccc gggtgttgcc ctgaattggc
                                                                        720
                                                                       780
ggccaaggan ccctgccccn g
                                                                       801
      <210> 17
      <211> 740
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(740)
      <223> n = A,T,C \text{ or } G
      <400> 17
gtgagagcca ggcgtccctc tgcctgccca ctcagtggca acacccggga gctgttttgt
```

```
cctttgtgga gcctcagcag ttccctcttt cagaactcac tgccaagagc cctgaacagg
                                                                        120
agccaccatg cagtgettea getteattaa gaccatgatg atcetettea atttgeteat
                                                                        180
ctttctgtgt ggtgcagccc tgttggcagt gggcatctgg gtgtcaatcg atggggcatc
                                                                        240
ctttctgaag atcttcgggc cactgtcgtc cagtgccatg cagtttgtca acgtgggcta
                                                                        300
cttcctcatc gcagccggcg ttgtggtctt tgctcttggt ttcctgggct gctatggtgc
                                                                       360
taagacggag agcaagtgtg ccctcgtgac gttcttcttc atcctcctcc tcatcttcat
                                                                        420
tgctgaagtt gcagctgctg tggtcgcctt ggtgtacacc acaatggctg aaccattcct
                                                                       480
gacgttgctg gtantgcctg ccatcaanaa agattatggg ttcccaggaa aaattcactc
                                                                       540
aantntggaa caccnccatg aaaagggctc caatttctgn tggcttcccc aactataccg
                                                                       600
qaattttgaa aganteneee taetteeaaa aaaaaanant tgeetttnee eeenttetgt
                                                                       660
tgcaatgaaa acntcccaan acngccaatn aaaacctgcc cnnncaaaaa ggntcncaaa
                                                                       720
caaaaaaant nnaagggttn
                                                                       740
      <210> 18
      <211> 802
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(802)
      <223> n = A, T, C or G
      <400> 18
ccgctggttg cgctggtcca gngnagccac gaagcacgtc agcatacaca gcctcaatca
                                                                        60
caaggtette cagetgeege acattacgea gggcaagage etceageaac actgeatatg
                                                                       120
ggatacactt tactttagca gccagggtga caactgagag gtgtcgaagc ttattcttct
                                                                       180
gagcctctgt tagtggagga agattccggg cttcagctaa gtagtcagcg tatgtcccat
                                                                       240
aagcaaacac tgtgagcagc cggaaggtag aggcaaagtc actctcagcc agctctctaa
                                                                       300
cattgggcat gtccagcagt tctccaaaca cgtagacacc agnggcctcc agcacctgat
                                                                       360
ggatgagtgt ggccagcgct gcccccttgg ccgacttggc taggagcaga aattgctcct
                                                                       420
ggttctgccc tgtcaccttc acttccgcac tcatcactgc actgagtgtg ggggacttgg
                                                                       480
gctcaggatg tccagagacg tggttccgcc ccctcnctta atgacaccgn ccanncaacc
                                                                       540
gtcggctccc gccgantgng ttcgtcgtnc ctgggtcagg gtctgctggc cnctacttgc
                                                                       600
aancttegte nggeeeatgg aatteacene aceggaactn gtangateea etnnttetat
                                                                       660
aaccggncgc caccgcnnnt ggaactccac tettnttncc tttacttgag ggttaaggte
                                                                       720
accettnneg ttacettggt ccaaacentn centgtgteg anatngtnaa tenggneena
                                                                       780
tnccancene atangaagee ng
                                                                       802
      <210> 19
      <211> 731
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(731)
      <223> n = A,T,C or G
      <400> 19
cnaagettee aggtnaeggg eegenaance tgaeeenagg tancanaang eagnengegg
                                                                        60
gagcccaccg tcacgnggng gngtctttat nggagggggc ggagccacat cnctggacnt
                                                                       120
entgacecca acteccence nencantgea gtgatgagtg cagaactgaa ggtnacgtgg
                                                                       180
caggaaccaa gancaaanne tgeteennte caagteggen nagggggegg ggetggeeac
                                                                       240
geneateent enagtgetgn aaageeeenn eetgtetaet tgtttggaga aengennnga
                                                                       300
```

```
catgcccagn gttanataac nggcngagag tnantttgcc tctcccttcc ggctgcgcan
 cgngtntgct tagnggacat aacctgacta cttaactgaa cccnngaatc tnccnccct
                                                                         360
 ccactaaget cagaacaaaa aacttegaca ccacteantt gteacetgne tgeteaagta
                                                                         420
 aagtgtaccc catneccaat gtntgetnga ngetetgnee tgenttangt teggteetgg
                                                                         480
 gaagacctat caattnaagc tatgtttctg actgcctctt gctccctgna acaancnacc
                                                                         540
 cnncnntcca aggggggnc ggcccccaat ccccccaacc ntnaattnan tttanccccn
                                                                         600
 cccccnggcc cggcctttta cnancntcnn nnacngggna aaaccnnngc tttncccaac
                                                                        660
                                                                        720
 nnaatccncc t
                                                                        731
       <210> 20
       <211> 754
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(754)
       <223> n = A,T,C or G
       <400> 20
 ttttttttt tttttttt taaaaacccc ctccattnaa tgnaaacttc cgaaattgtc
 caacccctc ntccaaatnn contttccgg gngggggttc caaacccaan ttanntttgg
                                                                         60
 annttaaatt aaatnttnnt tggnggnnna anccnaatgt nangaaagtt naacccanta
                                                                        120
 tnancttnaa tncctggaaa ccngtngntt ccaaaaatnt ttaaccctta antccctccg
                                                                        180
 aaatngttna nggaaaaccc aanttetent aaggttgttt gaaggntnaa tnaaaancce
                                                                        240
nnccaattgt ttttngccac gcctgaatta attggnttcc gntgttttcc nttaaaanaa
                                                                        300
ggnnancccc ggttantnaa tccccccnnc cccaattata ccganttttt ttngaattgg
                                                                        360
ganccenegg gaattaacgg ggnnnnteec tnttgggggg enggnneece eccenteggg
                                                                        420
ggttngggnc aggncnnaat tgtttaaggg tccgaaaaat ccctccnaga aaaaaanctc
                                                                        480
ccaggntgag nntngggttt ncccccccc canggcccct ctcgnanagt tggggtttgg
                                                                       540
ggggcctggg attttntttc ccctnttncc tcccccccc ccnggganag aggttngngt
                                                                       600
tttgntcnnc ggccccnccn aaganctttn ccganttnan ttaaatccnt gcctnggcga
                                                                       660
agtccnttgn agggntaaan ggccccctnn cggg
                                                                       720
                                                                       754
      <210> 21
      <211> 755
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(755)
      <223> n = A, T, C \text{ or } G
atcancccat gaccccnaac nngggaccnc tcanccggnc nnncnaccnc cggccnatca
nngtnagnnc actncnnttn natcacnccc cnccnactac gcccncnanc cnacgcncta
                                                                        60
nncanatncc actganngcg cgangtngan ngagaaanct nataccanag ncaccanacn
                                                                       120
ccagctgtcc nanaangcct nnnatacngg nnnatccaat ntgnancctc cnaagtattn
                                                                      180
nncnncanat gattttcctn ancegattac centnecece tanecectec eccecaacna
                                                                      240
cgaaggenet ggneenaagg nngegnenee eegetagnte eeenneaagt eneneneeta
                                                                      300
aactcancen nattaenege ttentgagta teactceeeg aateteacee taeteaaete
                                                                      360
aaaaanatcn gatacaaaat aatncaagcc tgnttatnac actntgactg ggtctctatt
                                                                      420
ttagnggtcc ntnaanchtc ctaatacttc cagtctncct tcnccaattt ccnaanggct
                                                                      480
ctttcngaca gcatnttttg gttcccnntt gggttcttan ngaattgccc ttcntngaac
                                                                      540
                                                                      600
```

```
gggctcntct tttccttcgg ttancctggn ttcnnccggc cagttattat ttcccntttt
                                                                       660
aaattentne entttanttt tggenttena aacceeegge ettgaaaaeg geeeeetggt
                                                                       720
aaaaggttgt tttganaaaa tttttgtttt gttcc
                                                                       755
      <210> 22
      <211> 849
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(849)
      \langle 223 \rangle n = A,T,C or G
      <400> 22
tttttttttt tttttangtg tngtcgtgca ggtagaggct tactacaant gtgaanacgt
                                                                        60
acgctnggan taangcgacc cganttctag gannencect aaaatcanac tgtgaagatn
                                                                       120
atcctgnnna cggaanggtc accggnngat nntgctaggg tgnccnctcc cannnenttn
                                                                       180
cataacteng nggeeetgee caccacette ggeggeeeng ngneegggee egggteattn
                                                                       240
gnnttaaccn cactnngcna neggttteen neecenneng accenggega teeggggtne
                                                                       300
tetgtettee cetgnagnen anaaantggg ceneggneee etttaceeet nnacaageea
                                                                       360
engeenteta neenengeee eccetecant nngggggaet geenannget eegttnetng
                                                                       420
nnaccccnnn gggtncctcg gttgtcgant cnaccgnang ccanggattc cnaaggaagg
                                                                       480
tgegttnttg gecectacce ttegetnegg nncaecette eegaenanga neegeteeeg
                                                                       540
enennegning cetenecteg caacaceege netentengt neggninece ecceaceege
                                                                       600
necetenene ngnegnanen eteeneenee gteteannea eeaceegee eegeeaggee
                                                                       660
ntcanccacn ggnngacnng nagenennte geneegegen gegneneet egeenengaa
                                                                       720
ctncntcngg ccantnncgc tcaancenna cnaaacgccg ctgcgcggcc cgnagcgncc
                                                                       780
necteenega gteeteeegn etteenacee angnntteen egaggacaen nnaceeegee
                                                                       840
nncangcgg
                                                                       849
      <210> 23
      <211> 872
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(872)
      <223> n = A,T,C or G
      <400> 23
gegeaaacta tacttegete gnactegtge geetegetne tettteete egeaaceatg
                                                                        60
tetgaenane eegattngge ngatatenan aagntegane agteeaaaet gantaacaea
                                                                       120
cacacnenan aganaaatee netgeettee anagtanaen attgaaenng agaaceange
                                                                       180
nggcgaatcg taatnaggcg tgcgccgcca atntgtcncc gtttattntn ccagcntcnc
                                                                       240
ctnccnaccc tacntetten nagetgtenn acceetngtn egnaceeccc naggteggga
                                                                       300
tegggtttnn nntgacegng enneceetee eccentecat nacganeene eegeaceaee
                                                                       360
nanngenege neceegnnet ettegeenee etgteetntn eeeetgtnge etggenengn
                                                                       420
accgcattga ccctcgccnn ctncnngaaa ncgnanacgt ccgggttgnn annancgctg
                                                                       480
tgggnnngcg tetgeneege gtteetteen nennetteea ceatettent taengggtet
                                                                       540
concecent tennneache ceteggacge thteethige ecceetinac teccecett
                                                                       600
cgncgtgncc cgnccccacc ntcatttnca nacgntcttc acaannncct ggntnnctcc
                                                                       660
cnancngncn gtcanccnag ggaagggngg ggnnccnntg nttgacgttg nggngangtc
                                                                       720
cgaanantcc tencentean enctaceeet egggegnnet etengttnee aacttaneaa
                                                                       780
```

```
ntctcccccg ngngcncntc tcagcctcnc ccnccccnct ctctgcantg tnctctgctc
                                                                         840
  tnaccnntac gantnttcgn cnccctcttt cc
                                                                         872
        <210> 24
        <211> 815
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc_feature
       <222> (1)...(815)
       <223> n = A,T,C or G
       <400> 24
 gcatgcaagc ttgagtattc tatagngtca cctaaatanc ttggcntaat catggtcnta
 nctgncttcc tgtgtcaaat gtatacnaan tanatatgaa tctnatntga caaganngta
                                                                         60
 tentneatta gtaacaantg tnntgteeat eetgtengan canatteeca tnnattnegn
                                                                        120
 cgcattcncn gcncantatn taatngggaa ntcnnntnnn ncaccnncat ctatcntncc
                                                                        180
 geneectgae tggnagagat ggatnantte tnntntgace nacatgttea tettggattn
                                                                        240
 aananccccc cgcngnccac cggttngnng cnagccnntc ccaagacctc ctgtggaggt
                                                                        300
 aacctgcgtc aganncatca aacntgggaa acccgcnncc angtnnaagt ngnnncanan
                                                                        360
 gatcccgtcc aggnttnacc atcccttcnc agcgcccct ttngtgcctt anagngnagc
                                                                        420
 gtgtccnanc cnctcaacat ganacgcgcc agnccanccg caattnggca caatgtcgnc
                                                                        480
 gaacccccta gggggantna tncaaanccc caggattgtc cncncangaa atcccncanc
                                                                        540
 ecencectae cennettigg gaengigaee aanteeegga gineeagiee ggeengnete
                                                                        600
 ccccaccggt nnccntgggg gggtgaanct cngnntcanc cngncgaggn ntcgnaagga
                                                                        660
accggneetn ggnegaanng anenntenga agngeenent egtataacce ceceteneca
                                                                        720
nccnacngnt agntcccccc cngggtncgg aangg
                                                                        780
                                                                        815
       <210> 25
       <211> 775
       <212> DNA
       <213> Homo sapien
      <220>
       <221> misc_feature
      <222> (1) ... (775)
      <223> n = A, T, C \text{ or } G
      <400> 25
ccgagatgtc tcgctccgtg gccttagctg tgctcgcgct actctctct tctggcctgg
aggctatcca gcgtactcca aagattcagg tttactcacg tcatccagca gagaatggaa
                                                                        60
agtcaaattt cctgaattgc tatgtgtctg ggtttcatcc atccgacatt gaanttgact
                                                                       120
tactgaagaa tgganagaga attgaaaaag tggagcattc agacttgtct ttcagcaagg
                                                                       180
actggtcttt ctatctcntg tactacactg aattcacccc cactgaaaaa gatgagtatg
                                                                       240
cctgccgtgt gaaccatgtg actttgtcac agcccaagat agttaagtgg gatcgagaca
                                                                       300
tgtaagcagn cnncatggaa gtttgaagat gccgcatttg gattggatga attccaaatt
                                                                       360
ctgcttgctt gcnttttaat antgatatgc ntatacaccc taccctttat gnccccaaat
                                                                       420
tgtaggggtt acatnantgt tcncntngga catgatette etttataant cencentteg
                                                                       480
aattgcccgt cncccngttn ngaatgtttc cnnaaccacg gttggctccc ccaggtcncc
                                                                       540
tettacggaa gggcctgggc enettincaa ggttggggga accnaaaatt tenetintge
                                                                       600
concoencea contettgng nocheanttt ggaaccette chatteeest tggeetenna
                                                                       660
nccttnncta anaaacttn aaancgtngc naaanntttn acttcccccc ttacc
                                                                       720
                                                                       775
```

<212> DNA

```
<211> 820
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(820)
       \langle 223 \rangle n = A,T,C or G
       <400> 26
anattantac agtgtaatct tttcccagag gtgtgtanag ggaacggggc ctagaggcat
                                                                         60
cccanagata nettatanea acagtgettt gaccaagage tgetgggeae attteetgea
                                                                        120
gaaaaggtgg cggtccccat cactcctcct ctcccatagc catcccagag gggtgagtag
                                                                        180
ccatcangcc ttcggtggga gggagtcang gaaacaacan accacagagc anacagacca
                                                                        240
ntgatgacca tgggcgggag cgagcctctt ccctqnaccq qqqtqqcana nqanaqccta
                                                                        300
nctgaggggt cacactataa acgttaacga ccnagatnan cacctgcttc aagtgcaccc
                                                                        360
ttcctacctg acnaccagng accnnnaact gengeetggg gacagenetg ggancageta
                                                                        420
acnnagcact cacctgcccc cccatggccg tncgcntccc tggtcctgnc aagggaagct
                                                                        480
ccctgttgga attncgggga naccaaggga nccccctcct ccanctgtga aggaaaaann
                                                                        540
gatggaattt tncccttccg gccnntcccc tcttccttta cacgccccct nntactcntc
                                                                        600
tecetetntt nteetgnene acttttnace cennnattte cettnattga teggannetn
                                                                        660
ganattccac thncgcctnc chtchatchg naanachaaa nacthtctna cccngggat
                                                                        720
gggnncctcg ntcatcctct ctttttcnct accnccnntt ctttgcctct ccttngatca
780tccaaccntc gntggccntn cccccccnnn tcctttnccc
820
       <210> 27
       <211> 818
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(818)
       \langle 223 \rangle n = A,T,C or G
       <400> 27
tctgggtgat ggcctcttcc tcctcaggga cctctgactg ctctgggcca aagaatctct
                                                                         60
tgtttcttct ccgagcccca ggcagcggtg attcagccct gcccaacctg attctgatga
                                                                        120
ctgcggatgc tgtgacggac ccaaggggca aatagggtcc cagggtccag ggaggggcgc
                                                                        180
ctgctgagca cttccgcccc tcaccctgcc cagcccctgc catgagctct gggctgggtc
                                                                        240
teegeeteea gggttetget etteeangea ngeeancaag tggegetggg ceacactgge
                                                                        300
ttetteetge ceenteeetg getetgante tetgtettee tgteetgtge angeneettg
                                                                        360
gatctcagtt tecetenete anngaactet gtttetgann tetteantta actntgantt
                                                                        420
tatnaccnan tggnctgtnc tgtcnnactt taatgggccn gaccggctaa tccctccctc
                                                                        480
netecettee anttennnna accngettne ententetee centaneceg eengggaane
                                                                        540
ctcctttgcc ctnaccangg gccnnnaccg cccntnnctn ggggggcnng gtnnctncnc
                                                                        600
etgntnnece enetenennt theetegtee ennennegen nngeanntte nengteeenn
                                                                        660
tnnctcttcn ngtntcgnaa ngntcncntn tnnnnngncn ngntnntncn tccctctcnc
                                                                        720
connitging thattanna acaganeece annacianna agganatana tetacacage
                                                                        780
cccnnccccc ngnattaagg cctccnntct ccggccnc
                                                                        818
       <210> 28
       <211> 731
```

```
<213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(731)
       <223> n = A,T,C or G
       <400> 28
 aggaagggcg gagggatatt gtangggatt gagggatagg agnataangg gggaggtgtg
                                                                         60
 teccaacatg anggtgnngt tetettttga angagggttg ngtttttann eenggtgggt
                                                                        120
 gattnaaccc cattgtatgg agnnaaaggn tttnagggat ttttcggctc ttatcagtat
                                                                        180
 ntanatteet ginaategga aaatnainti tennenggaa aaintigete eeateegnaa
 attnctcccg ggtagtgcat nttngggggn cngccangtt tcccaggctg ctanaatcgt
                                                                        240
 actaaagntt naagtgggan tncaaatgaa aacctnncac agagnatcen tacccgactg
                                                                        300
 tnnnttncct tcgccctntg actctgcnng agcccaatac ccnngngnat gtcncccngn
                                                                        360
 nnngcgnene tgaaannnne tegnggetnn ganeateang gggtttegea teaaaagenn
                                                                        420
 cgtttencat naaggeactt tngcctcate caacenetng ceetenneca tttngccgte
                                                                        480
nggttcncct acgctnntng cncctnnntn ganattttnc ccgcctnggg naancctcct
                                                                        540
gnaatgggta gggncttntc ttttnaccnn gnggtntact aatcnnctnc acgcntnctt
                                                                        600
tetenacece ecceetttt caateecane ggenaatggg gteteecenn egangggggg
                                                                        660
                                                                        720
nnncccannc c
                                                                        731
       <210> 29
       <211> 822
       <212> DNA
       <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(822)
      <223> n = A, T, C or G
      <400> 29
actagtccag tgtggtggaa ttccattgtg ttggggncnc ttctatgant antnttagat
cgctcanacc tcacancctc ccnacnangc ctataangaa nannaataga nctgtncnnt
                                                                        60
                                                                       120
atnthtache teatanneet ennnaceeae teeetettaa eeentaetgt geetatngen
tnnctantct ntgccgcctn cnanccaccn gtgggccnac cncnngnatt ctcnatctcc
                                                                       180
tenecatntn geetananta ngtneatace etatacetae necaatgeta nnnetaanen
                                                                       240
                                                                       300
tccatnantt annntaacta ccactgacnt ngactttcnc atnanctcct aatttgaatc
tactctgact cccacngcct annnattagc anchtccccc nachathtct caaccaaatc
                                                                       360
ntcaacaacc tatctanctg ttcnccaacc nttncctccg atccccnnac aaccccctc
                                                                       420
ccaaataccc nccacctgac ncctaacccn caccatcccg gcaagccnan ggncatttan
                                                                       480
ccactggaat cacnatngga naaaaaaaac ccnaactctc tancncnnat ctccctaana
                                                                       540
                                                                       600
aatnotootn naatttactn noantnocat caanoocacn tgaaacnnaa cocctgtttt
                                                                       660
tanatccctt ctttcgaaaa ccnaccettt annncccaac ctttngggcc cccccnctnc
ccnaatgaag gncncccaat cnangaaacg nccntgaaaa ancnaggcna anannntccg
                                                                       720
                                                                       780
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gtctgcagga tttgatgtct gaagtcgtgg agtgtggctt ggagctcctc atctacatna
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gctggaagcc ctggagggcc tctctcgcca gcctcccct tctctccacg ctctccangg
                                                                        240
acaccagggg ctccaggcag cccattattc ccagnangac atggtgtttc tccacgcgga
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cccatggggc ctgnaaggcc agggtctcct ttgacaccat ctctcccgtc ctgcctggca
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ggccgtggga tccactantt ctanaacggn cgccaccncg gtgggagctc cagctttqt
                                                                        420
tecenttaat gaaggttaat tgenegettg gegtaateat nggteanaae tnttteetgt
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gtgaaattgt ttntcccctc ncnattccnc ncnacatacn aacccggaan cataaagtgt
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taaagcctgg gggtngcctn nngaatnaac tnaactcaat taattgcgtt ggctcatggc
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ccgctttccn ttcnggaaaa ctgtcntccc ctgcnttnnt gaatcggcca cccccnggg
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aaaagcggtt tgcnttttng ggggntcctt ccncttcccc cctcnctaan ccctncqcct
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cggtcgttnc nggtngcggg gaangggnat nnnctcccnc naagggggng agnnngntat
                                                                        780
ccccaaa
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      <221> misc feature
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                                                                       120
aacaaaggac tcctgcagcc ttctctgtct gtctcttggc gcaggcacat ggggaggcct
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cccgcagggt gggggccacc agtccagggg tgggagcact acanggggtg ggagtgggtg
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gtggctggtn cnaatggcct gncacanatc cctacgattc ttgacacctg gatttcacca
                                                                       300
ggggaccttc tgttctccca nggnaacttc ntnnatctcn aaagaacaca actgtttctt
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engeanttet ggetgtteat ggaaageaca ggtgteenat ttnggetggg acttggtaca
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tatggttccg gcccacctct cccntcnaan aagtaattca ccccccccn ccntctnttq
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cctgggccct taantaccca caccggaact canttantta ttcatcttng gntgggcttq
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ntnatcnccn cctgaangcg ccaagttgaa aggccacgcc gtncccnctc cccatagnan
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nttttnncnt canctaatgc ccccccnggc aacnatccaa tccccccccn tgggggcccc
                                                                       660
agcccangge eccegneteg ggnnneengn enegnantee ecaggntete ecantengne
                                                                       720
connngence ecegeacgea gaacanaagg ntngageene egeannnnnn nggtnnenae
                                                                       780
ctcgccccc ccnncqnnq
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      <221> misc_feature
      <222> (1)...(789)
      <223> n = A, T, C or G
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 ggcaacaggc tccggcggcg gcggcggcgg ccctacctgc ggtaccaaat ntgcagcctc
                                                                      180
 cgctcccgct tgatnttcct ctgcagctgc aggatgccnt aaaacagggc ctcggccntn
 ggtgggcacc ctgggatttn aatttccacg ggcacaatgc ggtcgcancc cctcaccacc
                                                                      240
                                                                      300
 nattaggaat agtggtntta cccnccnccg ttggcncact ccccntggaa accacttntc
                                                                      360
 gcggctccgg catctggtct taaaccttgc aaacnctggg gccctctttt tggttantnt
                                                                      420
 ncengecaca ateatnacte agaetggene gggetggeee caaaaaanen eeccaaaace
                                                                      480
 ggnccatgtc ttnncggggt tgctgcnatn tncatcacct cccgggcnca ncaggncaac
 ccaaaagttc ttgnggcccn caaaaaanct ccggggggnc ccagtttcaa caaagtcatc
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 ccccttggcc cccaaatcct cccccgntt nctgggtttg ggaacccacg cctctnnctt
                                                                      600
 tggnnggcaa gntggntccc ccttcgggcc cccggtgggc ccnnctctaa ngaaaacncc
                                                                      660
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                                                                      720
                                                                      780
 cccccncg
                                                                      789
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       <223> n = A,T,C or G
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gactaaagtc tgatgaactt cccaatcaga tgagcatgga tgattggcca gaaatgaana
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agaagtttgc agatgtattt gcaaagaaga cgaaggcaga gtggtgtcaa atctttgacg
                                                                     180
                                                                     240
gcacagatgc ctgtgtgact ccggttctga cttttgagga ggttgttcat catgatcaca
acaangaacg gggctcgttt atcaccantg aggagcagga cgtgagcccc cgccctgcac
                                                                     300
                                                                     360
ctctgctgtt aaacacccca gccatccctt ctttcaaaag ggatccacta cttctagagc
ggncgccacc gcggtggagc tccagctttt gttcccttta gtgagggtta attgcgcgct
                                                                     420
tggcgtaatc atggtcatan ctgtttcctg tgtgaaattg ttatccgctc acaattccac
                                                                     480
                                                                     540
acaacatacg anccggaagc atmaaatttt aaagcctggm ggtmgcctaa tgamtgaact
nactcacatt aattggcttt gcgctcactg cccgctttcc agtccggaaa acctgtcctt
                                                                     600
gccagctgcc nttaatgaat cnggccaccc cccggggaaa aggcngtttg cttnttgggg
                                                                     660
egenettece getttetege tteetgaant cetteecece ggtetttegg ettgeggena
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                                                                     780
acggtatcna cct
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      <212> DNA
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      <220>
      <221> misc_feature
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      <223> n = A,T,C or G
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                                                                     60
                                                                    120
```

```
ccaaccacag ggaccaagct gaccaaacag cagctaattc tggcccgtga catactggag
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cageteaaat getaetaett tgattacaan gageagetee eegagteage etatatgeae
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cagcicitigg gccicaacci ccicticcig cigicccaga accgggiggc iganinccac
                                                                       360
acgganttgg ancggctgcc tgcccaanga catacanacc aatgtctaca tcnaccacca
                                                                       420
gtgtcctgga gcaatactga tgganggcag ctaccncaaa gtnttcctgg ccnagggtaa
                                                                       480
catececege egagagetae acettettea ttgacatect getegacaet ateagggatg
                                                                       540
aaaatcgcng ggttgctcca gaaaggctnc aanaanatcc ttttcnctga aggccccqq
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ttactgaggg ttnattgccg cccttggcgt tatcatggtc acnccngttn cctqtqttga
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                                                                       240
aaantccanc angtteteet tggtgaeete eeetteaaag ttgtteegge etteateaaa
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cttctnnaan angannancc canctttgtc gagctggnat ttgganaaca cgtcactgtt
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ttcttcagcc agttcacnat nttcatcagc ccctctgcca gctgttntat tccttggggg
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ggaancegte tetecettee tgaannaact ttgacegtng gaatageege genteneent
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achthetggg ccgggttcaa anteceteen ttgnennten eetegggeea ttetggattt
                                                                       720
nechaacttt tteetteece eneceenegg ngtttggntt ttteatnggg ecceaactet
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      <221> misc feature
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naacgccaac tcaggccatt cctaccaaag gaagaaaggc tggtctctcc acccctqta
                                                                       180
ggaaaggcct gccttgtaag acaccacaat ncggctgaat ctnaagtctt gtgttttact
                                                                       240
aatggaaaaa aaaaataaac aanaggtttt gttctcatgg ctgcccaccg cagcctggca
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ctaaaacanc ccagcgctca cttctgcttg ganaaatatt ctttgctctt ttggacatca
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```

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ggcttgatgg tatcactgcc acntttccac ccagctgggc ncccttcccc catntttgtc
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                                                                         480
 gcccctgaac ganatgcttc cancancett taagacccat aatcctngaa ccatggtgcc
                                                                         540
                                                                         600
 cttccggtct gatccnaaag gaatgttcct gggtcccant ccctcctttg ttncttacgt
 tgtnttggac centgetngn atnacecaan tganatecee ngaageacee tneeeetgge
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 atttganttt cntaaattct ctgccctacn nctgaaagca cnattccctn ggcnccnaan
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                                                                         60
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tenaanceae tegtgtattt tteacangea geeteeteeg aagenteegg geagttgggg
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gggctgacag gtgccagaac acactggatn ggcctttcca tggaagggcc tgggggaaat
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cncctnance caaactgcct ctcaaaggcc accttgcaca ccccgacagg ctagaaatgc
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actettette ccaaaaggtag ttgttettgt tgcccaagca neetecanca aaccaaaane
ttgcaaaatc tgctccgtgg gggtcatnnn taccanggtt ggggaaanaa acccggcngn
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gancencett gtttgaatge naaggnaata ateeteetgt ettgettggg tggaanagea
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caaattaatt ttgganttta aattaaatnt tnattngggg aanaanccaa atgtnaagaa
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aatttaaccc attatnaact taaatnoctn gaaaccontg gnttocaaaa atttttaacc
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cttaaatccc tccgaaattg ntaanggaaa accaaattcn cctaaggctn tttgaaggtt
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                                                                       300
ngatttaaac ccccttnant tnttttnacc cnngnctnaa ntatttngnt tccggtgttt
                                                                       360
teetnttaan entnggtaae teeegntaat gaannneeet aanceaatta aacegaattt
tttttgaatt ggaaattccn ngggaattna ccggggtttt tcccntttgg gggccatncc
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cccnctttcg gggtttgggn ntaggttgaa tttttnnang ncccaaaaaa ncccccaana
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aaaaaactcc caagnnttaa ttngaatntc ccccttccca ggccttttgg gaaaggnggg
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WO 00/04149 PCT/US99/15838

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tttntggggg congggantt onttoccon tinconcoc cocconqqt aaanqqttat
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ngnntttggt ttttgggccc cttnanggac cttccggatn gaaattaaat ccccqqqncq
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qccq
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      <221> misc_feature
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tttatttatt tttactgaaa gtgagaggga acttttgtgg cctttttcc ttttcctgta
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ggccgcctta agctttctaa atttggaaca tctaagcaag ctgaanggaa aagggggttt
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cgcaaaatca ctcgggggaa nggaaaggtt gctttgttaa tcatgcccta tqqtqqqtqa
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ttaactgctt gtacaattac ntttcacttt taattaattg tgctnaangc tttaattana
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teceggennt entigaaaca caengengaa ngtteteatt nteceenene cagginaaaa
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coctcaanon aattnetning coccegetore gentingtoe eneccegeget cogggaantin
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caccccnga annonntnnc naacnaaatt ccgaaaatat tcccnntcnc tcaattcccc
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ataaaaggtg cgcccccgca ccgttcanct cgcacttctc naanaccatg angttgggct
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ggancccata tetenacean tacteacent necececent gnnacecane ettetanngn
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 ttctttaaac cttgttcatt atgaacactg aaaataggaa tttgtgaaga gttaaaaagt
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 tgttaaactg tgatttttaa aaaatatcat ttgagaatat tctttcagag gtatttcat
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cctcttgaga ggtcagtaaa gaggacttaa tatttcatat ctacaaaatg accacaggat
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tgctgttgtt cttcttttta ccccatagct gagccactgc ctctgatttc aagaacctga
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agacgccctc agatcggtct tcccatttta ttaatcctgg gttcttgtct gggttcaaga
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acttggcagg ggggtcttgc tccttttca tatcaggtga ctctgcaaca ggaaggtgac
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WO 00/04149 PCT/US99/15838 ·· 21

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      <211> 590
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(590)
      <223> n = A, T, C or G
      <400> 46
actttttatt taaatgttta taaggcagat ctatgagaat gatagaaaac atggtgtgta
                                                                         60
atttgatagc aatattttgg agattacaga gttttagtaa ttaccaatta cacagttaaa
                                                                        120
aagaagataa tatattocaa goanatacaa aatatotaat gaaagatoaa ggoaggaaaa
                                                                        180
tgantataac taattgacaa tggaaaatca attttaatgt gaattgcaca ttatccttta
                                                                        240
aaagctttca aaanaaanaa ttattgcagt ctanttaatt caaacagtgt taaatggtat
                                                                        300
caggataaan aactgaaggg canaaagaat taattttcac ttcatgtaac ncacccanat
                                                                       360
ttacaatggc ttaaatgcan ggaaaaagca gtggaagtag ggaagtantc aaggtctttc
                                                                       420
tggtctctaa tctgccttac tctttgggtg tggctttgat cctctggaga cagctgccag
                                                                       480
ggctcctgtt atatccacaa tcccagcagc aagatgaagg gatgaaaaag gacacatgct
                                                                       540
gccttccttt gaggagactt catctcactg gccaacactc agtcacatgt
                                                                       590
      <210> 47
      <211> 774
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (774)
      \langle 223 \rangle n = A,T,C or G
      <400> 47
acaagggggc ataatgaagg agtggggana gattttaaag aaggaaaaaa aacgaggccc
                                                                        60
tgaacagaat tttcctgnac aacggggctt caaaataatt ttcttgggga ggttcaagac
                                                                       120
gcttcactgc ttgaaactta aatggatgtg ggacanaatt ttctgtaatg accctgaggg
                                                                       180
cattacagac gggactctgg gaggaaggat aaacagaaag gggacaaagg ctaatcccaa
                                                                       240
aacatcaaag aaaggaaggt ggcgtcatac ctcccagcct acacagttct ccagggctct
                                                                       300
```

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cctcatccct ggaggacgac agtggaggaa caactgacca tgtccccagg ctcctgtgtg
  ctggctcctg gtcttcagcc cccagctctg gaagcccacc ctctgctgat cctgcgtggc
                                                                          360
  ccacactcct tgaacacaca tccccaggtt atattcctgg acatggctga acctcctatt
                                                                          420
  cctacttccg agatgccttg ctccctgcag cctgtcaaaa tcccactcac cctccaaacc
                                                                          480
  acggcatggg aagcctttct gacttgcctg attactccag catcttggaa caatccctga
                                                                          540
  ttccccactc cttagaggca agatagggtg gttaagagta gggctggacc acttggagcc
                                                                          600
 aggetgetgg etteaaattn tggeteattt acgagetatg ggaeettggg caagtnatet
                                                                          660
 tcacttctat gggcntcatt ttgttctacc tgcaaaatgg gggataataa tagt
                                                                          720
                                                                         774
        <210> 48
        <211> 124
        <212> DNA
        <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(124)
       <223> n = A,T,C or G
       <400> 48
 canaaattga aattttataa aaaggcattt ttctcttata tccataaaat gatataattt
 ttgcaantat anaaatgtgt cataaattat aatgtteett aattacaget caacgcaact
                                                                          60
                                                                         120
 tggt
                                                                         124
       <210> 49
       <211> 147
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(147)
       \langle 223 \rangle n = A,T,C or G
       <400> 49
gccgatgcta ctattttatt gcaggaggtg ggggtgtttt tattattctc tcaacagctt
tgtggctaca ggtggtgtct gactgcatna aaaanttttt tacgggtgat tgcaaaaatt
                                                                         60
ttagggcacc catatcccaa gcantgt
                                                                        120
                                                                        147
      <210> 50
      <211> 107
      <212> DNA
      <213> Homo sapien
      <400> 50
acattaaatt aataaaagga ctgttggggt tctgctaaaa cacatggctt gatatattgc
atggtttgag gttaggagga gttaggcata tgttttggga gaggggt
                                                                        60
                                                                        107
      <210> 51
      <211> 204
      <212> DNA
      <213> Homo sapien
      <400> 51
gtcctaggaa gtctagggga cacacgactc tggggtcacg gggccgacac acttgcacgg
                                                                        60
```

```
cgggaaggaa aggcagagaa gtgacaccgt cagggggaaa tgacagaaag gaaaatcaag
                                                                        120
gccttgcaag gtcagaaagg ggactcaggg cttccaccac agccctgccc cacttggcca
                                                                        180
cctccctttt gggaccagca atgt
                                                                        204
      <210> 52
      <211> 491
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(491)
      <223> n = A,T,C or G
      <400> 52
acaaagataa catttatctt ataacaaaaa tttgatagtt ttaaaaggtta gtattgtgta
                                                                         60
gggtattttc caaaagacta aagagataac tcaggtaaaa agttagaaat gtataaaaca
                                                                        120
ccatcagaca ggtttttaaa aaacaacata ttacaaaatt agacaatcat ccttaaaaaa
                                                                        180
aaaacttctt gtatcaattt cttttgttca aaatgactga cttaantatt tttaaatatt
                                                                        240
tcanaaacac ttcctcaaaa attttcaana tggtagcttt canatgtncc ctcagtccca
                                                                        300
atgttgctca gataaataaa tctcgtgaga acttaccacc caccacaagc tttctggggc
                                                                        360
atgcaacagt gtcttttctt tnctttttct tttttttttt ttacaggcac agaaactcat
                                                                        420
caattttatt tggataacaa agggtctcca aattatattg aaaaataaat ccaagttaat
                                                                        480
atcactcttg t
                                                                        491
      <210> 53
      <211> 484
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(484)
      \langle 223 \rangle n = A,T,C or G
      <400> 53
acataattta gcagggctaa ttaccataag atgctattta ttaanaggtn tatgatctga
                                                                        60
gtattaacag tigcigaagt tiggiattit tatgcagcat titcittitg cittgataac
                                                                       120
actacagaac ccttaaggac actgaaaatt agtaagtaaa gttcagaaac attagctgct
                                                                       180
caatcaaatc tctacataac actatagtaa ttaaaacgtt aaaaaaaagt gttgaaatct
                                                                       240
gcactagtat anaccgctcc tgtcaggata anactgcttt ggaacagaaa gggaaaaanc
                                                                       300
agetttgant ttetttgtge tgatangagg aaaggetgaa ttacettgtt geeteteeet
                                                                       360
aatgattggc aggtcnggta aatnccaaaa catattccaa ctcaacactt cttttccncq
                                                                       420
tancttgant ctgtgtattc caggancagg cggatggaat gggccagccc ncggatgttc
                                                                       480
cant
                                                                       484
      <210> 54
      <211> 151
      <212> DNA
      <213> Homo sapien
      <400> 54
actaaacctc gtgcttgtga actccataca gaaaacggtg ccatccctga acacggctgg
                                                                        60
ccactgggta tactgctgac aaccgcaaca acaaaaacac aaatccttgg cactggctag
                                                                       120
tctatgtcct ctcaagtgcc tttttgtttg t
                                                                       151
```

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<210> 55
        <211> 91
        <212> DNA
        <213> Homo sapien
        <400> 55
 acctggcttg tctccgggtg gttcccggcg cccccacgg tccccagaac ggacactttc
                                                                           60
 gccctccagt ggatactcga gccaaagtgg t
                                                                           91
       <210> 56
       <211> 133
       <212> DNA
       <213> Homo sapien
       <400> 56
 ggcggatgtg cgttggttat atacaaatat gtcattttat gtaagggact tgagtatact
 tggatttttg gtatctgtgg gttgggggga cggtccagga accaataccc catggatacc
                                                                          60
 aagggacaac tgt
                                                                         120
                                                                         133
       <210> 57
       <211> 147
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(147)
       \langle 223 \rangle n = A,T,C or G
       <400> 57
actotggaga acctgagoog otgotoogoo totgggatga ggtgatgcan gongtggogo
gactgggagc tgagcccttc cctttgcgcc tgcctcagag gattgttgcc gacntgcana
                                                                          60
                                                                         120
tctcantggg ctggatncat gcagggt
                                                                         147
      <210> 58
      <211> 198
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(198)
      <223> n = A, T, C \text{ or } G
      <400> 58
acagggatat aggtttnaag ttattgtnat tgtaaaatac attgaatttt ctgtatactc
tgattacata catttatcct ttaaaaaaaga tgtaaatctt aatttttatg ccatctatta
                                                                         60
atttaccaat gagttacctt gtaaatgaga agtcatgata gcactgaatt ttaactagtt
                                                                        120
                                                                        180
ttgacttcta agtttggt
                                                                        198
      <210> 59
      <211> 330
      <212> DNA
      <213> Homo sapien
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<400> 59						
acaacaaatg ggt ccattgaaaa tta cacctgtgct agc tacagtcaat aaa cagaaggaat cta tttcgtcttt att	ttgctaa ( ttgctaa ( tgacaaa ( ttttatc (	tgattttaaa aatgggagtt gccagggcct acatggatct	tgacaagtta aactctagag acaggtggtt	tcaaaaactc caaatatagt tccagacttt	actcaatttt atcttctgaa ccagacccag	60 120 180 240 300 330
<210> 60 <211> 17 <212> DN <213> Ho	5	n			,	
<400> 60 accgtgggtg cct gtcgtgggct cct tcctggaacc agc <210> 61	tctacat t	catcctcatc	cagctggtgc	tgctcatcga	ctttqcqcac	60 120 175
<211> 15 <212> DN		ı				
accccacttt tcc ggttgttgct ctt tggactgcac agc	caacagt a	atcctcccct	ttccggatct	gctacatgat gctgagccgg	gagggtgagt acagcagtgc	60 120 154
<210> 62 <211> 30 <212> DN <213> Hor		ı				
<400> 62 cgctcgagcc cta	tagtgag t	cgtattaga				30
<210> 63 <211> 89 <212> DNZ <213> Hor		1				
<400> 63 acaagtcatt tcag ctgtatgaat aaaa	gcaccct t aatggtt a	tgctcttca tgtcaagt	aaactgacca	tcttttatat	ttaatgcttc	60 89
<210> 64 <211> 97 <212> DNA <213> Hor						
<400> 64 accggagtaa ctga aatcagtgca tcca	agtcggg a aggattg g	cgctgaatc tccttggat	tgaatccacc ctggggt	aataaataaa	ggttctgcag	60 97

```
<210> 65
        <211> 377
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc_feature
        <222> (1)...(377)
        <223> n = A,T,C or G
        <400> 65
 acaacaanaa ntcccttctt taggccactg atggaaacct ggaaccccct tttgatggca
 gcatggcgtc ctaggccttg acacagcggc tggggtttgg gctntcccaa accgcacacc
                                                                         60
 ccaaccctgg tctacccaca nttctggcta tgggctgtct ctgccactga acatcagggt
                                                                        120
 tcggtcataa natgaaatcc caanggggac agaggtcagt agaggaagct caatgagaaa
                                                                        180
 ggtgctgttt gctcagccag aaaacagctg cctggcattc gccgctgaac tatgaacccg
                                                                        240
 tgggggtgaa ctacccccan gaggaatcat gcctgggcga tgcaanggtg ccaacaggag
                                                                        300
                                                                        360
 gggcgggagg agcatgt
                                                                        377
       <210> 66
       <211> 305
       <212> DNA
       <213> Homo sapien
       <400> 66
 acgcctttcc ctcagaattc agggaagaga ctgtcgcctg ccttcctccg ttgttgcgtg
 agaacccgtg tgccccttcc caccatatcc accctcgctc catctttgaa ctcaaacacg
                                                                         60
 aggaactaac tgcaccctgg tecteteec agtececagt teacceteca teceteacet
                                                                        120
 tectecacte taagggatat caacactgee cageacaggg geeetgaatt tatgtggttt
                                                                        180
 ttatatattt tttaataaga tgcactttat gtcatttttt aataaagtct gaagaattac
                                                                        240
                                                                        300
 tgttt
                                                                        305
       <210> 67
       <211> 385
       <212> DNA
       <213> Homo sapien
       <400> 67
actacacaca ctccacttgc ccttgtgaga cactttgtcc cagcacttta ggaatgctga
ggtcggacca gccacatctc atgtgcaaga ttgcccagca gacatcaggt ctgagagttc
                                                                        60
cccttttaaa aaaggggact tgcttaaaaa agaagtctag ccacgattgt gtagagcagc
                                                                       120
tgtgctgtgc tggagattca cttttgagag agttctcctc tgagacctga tctttagagg
                                                                       180
ctgggcagtc ttgcacatga gatggggctg gtctgatctc agcactcctt agtctgcttg
                                                                       240
cctctcccag ggccccagcc tggccacacc tgcttacagg gcactctcag atgcccatac
                                                                       300
                                                                       360
catagittci gigciagigg accgi
                                                                       385
      <210> 68
      <211> 73
      <212> DNA
      <213> Homo sapien
      <400> 68
acttaaccag atatatttt accccagatg gggatattct ttgtaaaaaa tgaaaataaa
                                                                       60
gtttttttaa tgg
                                                                       73
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WO 00/04149 PCT/US99/15838 27

```
<210> 69
      <211> 536
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(536)
      <223> n = A,T,C or G
      <400> 69
actagtccag tgtggtggaa ttccattgtg ttgggggctc tcaccctcct ctcctgcagc
                                                                        60
tccagctttg tgctctgcct ctgaggagac catggcccag catctgagta ccctgctgct
                                                                       120
cctgctggcc accctagctg tggccctggc ctggagcccc aaggaggagg ataggataat
                                                                       180
cccgggtggc atctataacg cagacctcaa tgatgagtgg gtacagcgtg cccttcactt
                                                                       240
cqccatcagc gagtataaca aggccaccaa agatgactac tacagacgtc cgctgcgggt
                                                                       300
actaagagcc aggcaacaga ccgttggggg ggtgaattac ttcttcgacg tagaggtggg
                                                                       360
ccgaaccata tgtaccaagt cccagcccaa cttggacacc tgtgccttcc atgaacagcc
                                                                       420
agaactgcag aagaaacagt tgtgctcttt cgagatctac gaagttccct ggggagaaca
                                                                       480
gaangtccct gggtgaaatc caggtgtcaa gaaatcctan ggatctgttg ccaggc
                                                                       536
      <210> 70
      <211> 477
      <212> DNA
      <213> Homo sapien
     <400> 70
atgaccccta acaggggccc tctcagccct cctaatgacc tccggcctag ccatgtgatt
                                                                        60
tcacttccac tccataacgc tcctcatact aggcctacta accaacacac taaccatata
                                                                       120
ccaatgatgg cgcgatgtaa cacgagaaag cacataccaa ggccaccaca caccacctgt
                                                                       180
ccaaaaaggc cttcgatacg ggataatcct atttattacc tcagaagttt ttttcttcgc
                                                                       240
agggattttt ctgagccttt taccactcca gcctagcccc taccccccaa ctaggagggc
                                                                       300
actggccccc aacaggcatc accccgctaa atcccctaga agtcccactc ctaaacacat
                                                                       360
ccgtattact cgcatcagga gtatcaatca cctgagctca ccatagtcta atagaaaaca
                                                                       420
accgaaacca aattattcaa agcactgctt attacaattt tactgggtct ctatttt
                                                                       477
      <210> 71
      <211> 533
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(533)
      <223> n = A, T, C \text{ or } G
      <400> 71
agagetatag gtacagtgtg ateteagett tgcaaacaca ttttetacat agatagtact
                                                                        60
aggtattaat agatatgtaa agaaagaaat cacaccatta ataatggtaa gattggttta
                                                                       120
tgtgatttta gtggtatttt tggcaccctt atatatgttt tccaaacttt cagcagtgat
                                                                       180
attatttcca taacttaaaa agtgagtttg aaaaagaaaa tctccagcaa gcatctcatt
                                                                       240
taaataaagg tttgtcatct ttaaaaaatac agcaatatgt gactttttaa aaaagctgtc
                                                                       300
aaataggtgt gaccctacta ataattatta gaaatacatt taaaaaacatc gagtacctca
                                                                       360
agtcagtttg ccttgaaaaa tatcaaatat aactcttaga gaaatgtaca taaaagaatg
                                                                       420
cttcgtaatt ttggagtang aggttccctc ctcaattttg tatttttaaa aagtacatgg
                                                                       480
taaaaaaaaa aattcacaac agtatataag gctgtaaaat gaagaattct gcc
                                                                       533
```

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<210> 72
       <211> 511
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(511)
       <223> n = A,T,C \text{ or } G
       <400> 72
 tattacggaa aaacacacca cataattcaa ctancaaaga anactgcttc agggcgtgta
 aaatgaaagg cttccaggca gttatctgat taaagaacac taaaagaggg acaaggctaa
                                                                       60
 aagccgcagg atgtctacac tatancaggc gctatttggg ttggctggag gagctgtgga
                                                                      120
 aaacatggan agattggtgc tgganatcgc cgtggctatt cctcattgtt attacanagt
                                                                      180
 gaggttctct gtgtgcccac tggtttgaaa accgttctnc aataatgata gaatagtaca
                                                                      240
 cacatgagaa ctgaaatggc ccaaacccag aaagaaagcc caactagatc ctcagaanac
                                                                      300
 gcttctaggg acaataaccg atgaagaaaa gatggcctcc ttgtgccccc gtctgttatg
                                                                      360
 atttctctcc attgcagcna naaacccgtt cttctaagca aacncaggtg atgatggcna
                                                                      420
                                                                      480
 aaatacaccc cctcttgaag naccnggagg a
                                                                      511
       <210> 73
       <211> 499
       <212> DNA
       <213> Homo sapien
       <220>
      <221> misc_feature
      <222> (1)...(499)
      \langle 223 \rangle n = A,T,C or G
      <400> 73
cagtgccagc actggtgcca gtaccagtac caataacagt gccagtgcca gtgccagcac
cagtggtggc ttcagtgctg gtgccagcct gaccgccact ctcacatttg ggctcttcgc
                                                                      60
tggccttggt ggagctggtg ccagcaccag tggcagctct ggtgcctgtg gtttctccta
                                                                     120
caagtgagat tttagatatt gttaatcctg ccagtctttc tcttcaagcc agggtgcatc
                                                                     180
ctcagaaacc tactcaacac agcactctag gcagccacta tcaatcaatt gaagttgaca
                                                                     240
300
antctagagg gcccgtttaa acccgctgat cagcctcgac tgtgccttct anttgccagc
                                                                     360
catctgttgt ttgcccctcc cccgntgcct tccttgaccc tggaaagtgc cactcccact
                                                                     420
                                                                     480
gtcctttcct aantaaaat
                                                                     499
      <210> 74
      <211> 537
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(537)
      <223> n = A,T,C \text{ or } G
      <400> 74
tttcatagga gaacacactg aggagatact tgaagaattt ggattcagcc gcgaagagat
```

```
ttatcagctt aactcagata aaatcattga aagtaataag gtaaaagcta gtctctaact
                                                                       120
tccaggccca cggctcaagt gaatttgaat actgcattta cagtgtagag taacacataa
                                                                       180
cattgtatgc atggaaacat ggaggaacag tattacagtg tcctaccact ctaatcaaga
                                                                       240
aaagaattac agactctgat tctacagtga tgattgaatt ctaaaaatgg taatcattag
                                                                       300
ggcttttgat ttataanact ttgggtactt atactaaatt atggtagtta tactgccttc
                                                                       360
cagtttgctt gatatatttg ttgatattaa gattcttgac ttatattttg aatgggttct
                                                                       420
actgaaaaan gaatgatata ttottgaaga catcgatata catttattta cactottgat
                                                                       480
tctacaatgt agaaaatgaa ggaaatgccc caaattgtat ggtgataaaa gtcccgt
                                                                       537
      <210> 75
      <211> 467
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (467)
      <223> n = A,T,C or G
      <400> 75
caaanacaat tgttcaaaag atgcaaatga tacactactg ctgcagctca caaacacctc
                                                                        60
tgcatattac acgtacctcc tcctgctcct caagtagtgt ggtctatttt gccatcatca
                                                                       120
cctgctgtct gcttagaaga acggctttct gctgcaangg agagaaatca taacagacgg
                                                                       180
tggcacaagg aggccatctt ttcctcatcg gttattgtcc ctagaagcgt cttctgagga
                                                                       240
tctagttggg ctttctttct gggtttgggc catttcantt ctcatgtgtg tactattcta
                                                                       300
tcattattgt ataacggttt tcaaaccngt gggcacncag agaacctcac tctgtaataa
                                                                       360
caatgaggaa tagccacggt gatctccagc accaaatctc tccatgttnt tccagagctc
                                                                       420
ctccagccaa cccaaatagc cgctgctatn gtgtagaaca tccctgn
                                                                       467
      <210> 76
      <211> 400
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(400)
      \langle 223 \rangle n = A,T,C or G
      <400> 76
aagetgaeag cattegggee gagatgtete geteegtgge ettagetgtg etegegetae
                                                                        60
tetetettte tggeetggag getatecage gtaetecaaa gatteaggtt taeteacgte
                                                                       120
atccagcaga gaatggaaag tcaaatttcc tgaattgcta tgtgtctggg tttcatccat
                                                                       180
ccgacattga agttgactta ctgaagaatg gagagagaat tgaaaaagtg gagcattcag
                                                                       240
acttgtcttt cagcaaggac tggtctttct atctcttgta ctacactgaa ttcacccca
                                                                       300
ctgaaaaaga tgagtatgcc tgccgtgtga accatgtgac tttgtcacag cccaagatng
                                                                       360
ttnagtggga tcganacatg taagcagcan catgggaggt
                                                                       400
      <210> 77
      <211> 248
      <212> DNA
      <213> Homo sapien
      <400> 77
ctggagtgcc ttggtgtttc.aagcccctgc aggaagcaga atgcaccttc tgaggcacct
                                                                        60
```

```
ccagctgccc cggcggggga tgcgaggctc ggagcaccct tgcccggctg tgattgctgc
  caggcactgt tcatctcagc ttttctgtcc ctttgctccc ggcaagcgct tctgctgaaa
                                                                         120
  gttcatatct ggagcctgat gtcttaacga ataaaggtcc catgctccac ccgaaaaaaa
                                                                         180
                                                                         240
  aaaaaaaa
                                                                         248
        <210> 78
        <211> 201
        <212> DNA
        <213> Homo sapien
        <400> 78
 actagtccag tgtggtggaa ttccattgtg ttgggcccaa cacaatggct acctttaaca
 teacceagae ecegecetge ecgtgeecea egetgetget aacgacagta tgatgettae
                                                                         60
 tetgetacte ggaaactatt tttatgtaat taatgtatge tttettgttt ataaatgeet
                                                                        120
                                                                        180
 gatttaaaaa aaaaaaaaa a
                                                                        201
       <210> 79
       <211> 552
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(552)
       <223> n = A, T, C or G
       <400> 79
tccttttgtt aggtttttga gacaacccta gacctaaact gtgtcacaga cttctgaatg
tttaggcagt gctagtaatt tcctcgtaat gattctgtta ttactttcct attctttatt
                                                                         60
cctctttctt ctgaagatta atgaagttga aaattgaggt ggataaatac aaaaaggtag
                                                                        120
tgtgatagta taagtatcta agtgcagatg aaagtgtgtt atatatatcc attcaaaatt
                                                                        180
atgcaagtta gtaattactc agggttaact aaattacttt aatatgctgt tgaacctact
                                                                        240
ctgttccttg gctagaaaaa attataaaca ggactttgtt agtttgggaa gccaaattga
                                                                        300
taatattcta tgttctaaaa gttgggctat acataaanta tnaagaaata tggaatttta
                                                                        360
ttcccaggaa tatggggttc atttatgaat antacccggg anagaagttt tgantnaaac
                                                                       420
cngttttggt taatacgtta atatgtcctn aatnaacaag gcntgactta tttccaaaaa
                                                                       480
                                                                       540
aaaaaaaaa aa
                                                                       552
      <210> 80
      <211> 476
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(476)
      <223> n = A, T, C or G
      <400> 80
acagggattt gagatgctaa ggccccagag atcgtttgat ccaaccctct tattttcaga
ggggaaaatg gggcctagaa gttacagagc atctagctgg tgcgctggca cccctggcct
                                                                        60
cacacagact cccgagtagc tgggactaca ggcacacagt cactgaagca ggccctgttt
                                                                       120
gcaattcacg ttgccacctc caacttaaac attcttcata tgtgatgtcc ttagtcacta
                                                                       180
aggttaaact ttcccaccca gaaaaggcaa cttagataaa atcttagagt actttcatac
                                                                       240
tettetaagt cetettecag ceteactitg agteeteett gggggttgat aggaaninte
                                                                       300
                                                                       360
```

```
tcttggcttt ctcaataaaa tctctatcca tctcatgttt aatttggtac gcntaaaaat
                                                                       420
gctgaaaaaa ttaaaatgtt ctggtttcnc tttaaaaaaaa aaaaaaaaa aaaaaa
                                                                       476
      <210> 81
      <211> 232
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(232)
      <223> n = A,T,C or G
      <400> 81
tttttttttg tatgccntcn ctgtggngtt attgttgctg ccaccctgga ggagcccagt
                                                                        60
ttcttctgta tctttctttt ctgggggatc ttcctggctc tgcccctcca ttcccaqcct
                                                                       120
ctcatcccca tcttgcactt ttgctagggt tggaggcgct ttcctggtag cccctcagag
                                                                       180
actcagtcag cgggaataag tcctaggggt ggggggtgtg gcaagccggc ct
                                                                       232
      <210> 82
      <211> 383
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(383)
      <223> n = A,T,C or G
      <400> 82
aggcgggagc agaagctaaa gccaaagccc aagaagagtg gcagtgccag cactggtgcc
                                                                        60
agtaccagta ccaataacat gccagtgcca gtgccagcac cagtggtggc ttcagtgctg
                                                                       120
gtgccagcct gaccgccact ctcacatttg ggctcttcgc tggccttggt ggagctggtg
                                                                       180
ccagcaccag tggcagctct ggtgcctgtg gtttctccta caagtgagat tttagatatt
                                                                       240
gttaatcctg ccagtctttc tcttcaagcc agggtgcatc ctcagaaacc tactcaacac
                                                                       300
agcactcing gcagccacta tcaatcaatt gaagtigaca cicigcatta aatctatitg
                                                                       360
ccatttcaaa aaaaaaaaaa aaa
                                                                       383
     <210> 83
     <211> 494
     <212> DNA
     <213> Homo sapien
     <220>
      <221> misc feature
      <222> (1)...(494)
      <223> n = A,T,C or G
      <400> 83
accgaattgg gaccgctggc ttataagcga tcatgtcctc cagtattacc tcaacgagca
                                                                       60
gggagatcga gtctatacgc tgaagaaatt tgacccgatg ggacaacaga cctgctcagc
                                                                       120
ccatcctgct cggttctccc cagatgacaa atactctcga caccgaatca ccatcaagaa
                                                                      180
acgetteaag gtgeteatga eccageaace gegeeetgte etetgagggt eettaaactg
                                                                      240
atgtetttte tgecacetgt tacceetegg agaeteegta accaaactet teggaetgtg
                                                                      300
agccctgatg cctttttgcc agccatactc tttggcntcc agtctctcgt ggcgattgat
                                                                      360
```

```
tatgcttgtg tgaggcaatc atggtggcat cacccatnaa gggaacacat ttganttttt
 tttcncatat tttaaattac naccagaata nttcagaata aatgaattga aaaactctta
                                                                         420
                                                                         480
 aaaaaaaaa aaaa
                                                                         494
       <210> 84
       <211> 380
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(380)
       <223> n = A, T, C or G
       <400> 84
gctggtagcc tatggcgtgg ccacggangg gctcctgagg cacgggacag tgacttccca
agtatectge geogegtett ctacegtece tacetgeaga tettegggea gatteceeag
                                                                         60
gaggacatgg acgtggccct catggagcac agcaactgct cgtcggagcc cggcttctgg
                                                                        120
gcacaccete etggggeeea ggegggeace tgegteteee agtatgeeaa etggetggtg
                                                                        180
gtgctgctcc tcgtcatctt cctgctcgtg gccaacatcc tgctggtcac ttgctcattg
                                                                        240
ccatgttcag ttacacattc ggcaaagtac agggcaacag cnatctctac tgggaaggcc
                                                                        300
                                                                        360
agcgttnccg cctcatccgg
                                                                        380
      <210> 85
      <211> 481
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(481)
      <223> n = A,T,C or G
      <400> 85
gagttagete etceacaace tigatgaggt egtetgeagt ggeetetege ticatacege
tnccatcgtc atactgtagg tttgccacca cctcctgcat cttggggcgg ctaatatcca
                                                                        60
ggaaactctc aatcaagtca ccgtcnatna aacctgtggc tggttctgtc ttccgctcgg
                                                                       120
tgtgaaagga tctccagaag gagtgctcga tcttccccac acttttgatg actttattga
                                                                       180
gtcgattctg catgtccagc aggaggttgt accagctctc tgacagtgag gtcaccagcc
                                                                       240
ctatcatgcc nttgaacgtg ccgaagaaca ccgagccttg tgtggggggt gnagtctcac
                                                                       300
ccagattctg cattaccaga nagccgtggc aaaaganatt gacaactcgc ccaggnngaa
                                                                       360
aaagaacacc tcctggaagt gctngccgct cctcgtccnt tggtggnngc gcntnccttt
                                                                       420
                                                                       480
t
                                                                       481
      <210> 86
      <211> 472
      <212> DNA
      <213> Homo sapien
     <220>
     <221> misc_feature
      <222> (1)...(472)
     <223> n = A, T, C or G
     <400> 86
```

```
aacatcttcc tgtataatgc tgtgtaatat cgatccgatn ttgtctgctg agaattcatt
                                                                         60
acttggaaaa gcaacttnaa gcctggacac tggtattaaa attcacaata tgcaacactt
                                                                        120
taaacagtgt gtcaatctgc tcccttactt tgtcatcacc agtctgggaa taagggtatg
                                                                        180
ccctattcac acctgttaaa agggcgctaa gcatttttga ttcaacatct ttttttttga
                                                                        240
cacaagtccg aaaaaagcaa aagtaaacag ttnttaattt gttagccaat tcactttctt
                                                                        300
catgggacag agccatttga tttaaaaagc aaattgcata atattgagct ttgggaqctq
                                                                        360
atatntgagc ggaagantag cetttetact teaceagaca caacteettt catattggga
                                                                        420
tgttnacnaa agttatgtct cttacagatg ggatgctttt gtggcaattc tg
                                                                        472
      <210> 87
      <211> 413
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (413)
      <223> n = A,T,C or G
      <400> 87
agaaaccagt atctctnaaa acaacctctc ataccttgtg gacctaattt tgtgtgcgtg
                                                                        60
tgtgtgtgcg cgcatattat atagacaggc acatcttttt tacttttgta aaagcttatg
                                                                        120
cctctttggt atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct
                                                                        180
ttgtcttctg tgtaaatggt actagagaaa acacctatnt tatgagtcaa tctagttngt
                                                                        240
tttattcgac atgaaggaaa tttccagatn acaacactna caaactctcc cttgactagg
                                                                       300
ggggacaaag aaaagcanaa ctgaacatna gaaacaattn cctggtgaga aattncataa
                                                                       360
acagaaattg ggtngtatat tgaaananng catcattnaa acgttttttt ttt
                                                                       413
      <210> 88
      <211> 448
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(448)
      \langle 223 \rangle n = A,T,C or G
      <400> 88
cgcagcgggt cctctctatc tagctccagc ctctcgcctg ccccactccc cgcgtcccgc
                                                                        60
gtectageen accatggeeg ggeeeetgeg egeeeegetg etectgetgg ceateetgge
                                                                       120
cgtggccctg gccgtgagcc ccgcggccgg ctccagtccc ggcaagccgc cgcgcctggt
                                                                       180
gggaggccca tggaccccgc gtggaagaag aaggtgtgcg gcgtgcactg gactttqccq
                                                                       240
teggenanta caacaaacce geaacnaett ttacenagen egegetgeag gttgtgeege
                                                                       300
cccaancaaa ttgttactng gggtaantaa ttcttggaag ttgaacctgg gccaaacnng
                                                                       360
tttaccagaa ccnagccaat tngaacaatt ncccctccat aacagcccct tttaaaaaagg
                                                                       420
gaancantcc tgntcttttc caaatttt
                                                                       448
      <210> 89
      <211> 463
      <212> DNA
      <213> Homo sapien
      <221> misc_feature
```

```
<222> (1)...(463)
        <223> n = A, T, C \text{ or } G
 gaattttgtg cactggccac tgtgatggaa ccattgggcc aggatgcttt gagtttatca
 gtagtgattc tgccaaagtt ggtgttgtaa catgagtatg taaaatgtca aaaaattagc
                                                                           60
 agaggtctag gtctgcatat cagcagacag tttgtccgtg tattttgtag ccttgaagtt
                                                                          120
 ctcagtgaca agttnnttct gatgcgaagt tctnattcca gtgttttagt cctttgcatc
                                                                          180
 tttnatgttn agacttgcct ctntnaaatt gcttttgtnt tctgcaggta ctatctgtgg
                                                                          240
 tttaacaaaa tagaannact tctctgcttn gaanatttga atatcttaca tctnaaaatn
                                                                          300
 aattetetee ecatannaaa acceangeee ttggganaat ttgaaaaang gnteettenn
                                                                          360
 aattennana antteagntn teatacaaca naaenggane eee
                                                                          420
                                                                          463
       <210> 90
       <211> 400
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(400)
       \langle 223 \rangle n = A,T,C or G
       <400> 90
agggattgaa ggtctnttnt actgtcggac tgttcancca ccaactctac aagttgctgt
cttccactca ctgtctgtaa gcntnttaac ccagactgta tcttcataaa tagaacaaat
                                                                          60
tetteaceag teacatette taggacettt ttggatteag ttagtataag etetteeact
                                                                         120
teetttgtta agaetteate tggtaaagte ttaagttttg tagaaaggaa tttaattget
                                                                         180
cgttctctaa caatgtcctc tccttgaagt atttggctga acaacccacc tnaagtccct
                                                                         240
trgtgcatcc attttaaata tacttaatag ggcattggtn cactaggtta aattctgcaa
                                                                         300
                                                                         360
gagtcatctg tctgcaaaag ttgcgttagt atatctgcca
                                                                         400
       <210> 91
       <211> 480
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(480)
      \langle 223 \rangle n = A,T,C or G
      <400> 91
gageteggat ecaataatet ttgtetgagg geageacaea tatneagtge eatggnaact
ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac
                                                                         60
atgeetettt gaetaeegtg tgeeagtget ggtgattete acaeacetee nneegetett
                                                                        120
tgtggaaaaa ctggcacttg nctggaacta gcaagacatc acttacaaat tcacccacga
                                                                        180
gacacttgaa aggtgtaaca aagcgactct tgcattgctt tttgtccctc cggcaccagt
                                                                        240
tgtcaatact aaccegetgg tttgccteca teacatttgt gatetgtage tetggataca
                                                                        300
totootgaca gtactgaaga acttottott ttgtttcaaa agcaactott ggtgootgtt
                                                                        360
ngatcaggtt cccatttccc agtccgaatg ttcacatggc atatnttact tcccacaaaa
                                                                        420
                                                                        480
      <210> 92
      <211> 477
      <212> DNA
```

```
<213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(477)
      <223> n = A, T, C \text{ or } G
      <400> 92
atacagecca nateceacea egaagatgeg ettgttgaet gagaacetga tgeggteact
                                                                         60
ggtcccgctg tagccccagc gactctccac ctgctggaag cggttgatgc tgcactcctt
                                                                        120
cccacgcagg cagcagcggg gccggtcaat gaactccact cgtggcttgg ggttgacggt
                                                                        180
taantgcagg aagaggctga ccacctcgcg gtccaccagg atgcccgact gtgcgggacc
                                                                        240
tgcagcgaaa ctcctcgatg gtcatgagcg ggaagcgaat gangcccagg gccttgccca
                                                                        300
gaaccttccg cetgttctct ggcgtcacct gcagctgctg ccgctnacac tcggcctcgq
                                                                        360
accageggae aaacggegtt gaacageege aceteaegga tgeecantgt gtegegetee
                                                                        420
aggaacggcn ccagcgtgtc caggtcaatg tcggtgaanc ctccgcgggt aatggcg
                                                                        477
      <210> 93
      <211> 377
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(377)
      <223> n = A,T,C or G
      <400> 93
gaacggctgg accttgcctc gcattgtgct gctggcagga ataccttggc aagcagctcc
                                                                         60
agteegagea geceeagace getgeegeee gaagetaage etgeetetgg cetteecete
                                                                        120
egecteaatg cagaaccant agtgggagea etgtgtttag agttaagagt gaacactgtn
                                                                        180
tgattttact tgggaatttc ctctgttata tagcttttcc caatgctaat ttccaaacaa
                                                                        240
caacaacaaa ataacatgtt tgcctgttna gttgtataaa agtangtgat tctgtatnta
                                                                        300
aagaaaatat tactgttaca tatactgctt gcaanttctg tatttattgg tnctctggaa
                                                                       . 360
ataaatatat tattaaa
                                                                        377
      <210> 94
      <211> 495
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(495)
      <223> n = A, T, C \text{ or } G
      <400> 94
ccctttgagg ggttagggtc cagttcccag tggaagaaac aggccaggag aantgcgtgc
                                                                        60
cgagctgang cagatttece acagtgacce cagageeetg ggetatagte tetgacceet
                                                                       120
ccaaggaaag accaccttct ggggacatgg gctggagggc aggacctaga ggcaccaagg
                                                                       180
gaaggcccca ttccggggct gttccccgag gaggaaggga aggggctctg tgtgccccc
                                                                       240
acgaggaana ggccctgant cctgggatca nacacccctt cacgtgtatc cccacacaaa
                                                                       300
tgcaagetca ccaaggteee eteteagtee etteeetaca eeetgaaegg neaetggeee
                                                                       360
acacccaccc agancancca cccgccatgg ggaatgtnct caaggaatcg cngggcaacg
                                                                       420
tggactctng tcccnnaagg gggcagaatc tccaatagan gganngaacc cttgctnana
                                                                       480
```

```
aaaaaaana aaaaa
                                                                           495
        <210> 95
        <211> 472
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc_feature
        <222> (1)...(472)
        \langle 223 \rangle n = A,T,C or G
        <400> 95
 ggttacttgg tttcattgcc accacttagt ggatgtcatt tagaaccatt ttgtctgctc
 cctctggaag ccttgcgcag agcggacttt gtaattgttg gagaataact gctgaatttt
                                                                           60
 tagctgtttt gagttgattc gcaccactgc accacaactc aatatgaaaa ctatttnact
                                                                          120
 tatttattat cttgtgaaaa gtatacaatg aaaattttgt tcatactgta tttatcaagt
                                                                          180
 atgatgaaaa gcaatagata tatattettt tattatgttn aattatgatt gccattatta
                                                                          240
 atcggcaaaa tgtggagtgt atgttctttt cacagtaata tatgcctttt gtaacttcac
                                                                          300
 ttggttattt tattgtaaat gaattacaaa attcttaatt taagaaaatg gtangttata
                                                                         360
 tttanttcan taatttcttt ccttgtttac gttaattttg aaaagaatgc at
                                                                         420
                                                                         472
       <210> 96
       <211> 476
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(476)
       \langle 223 \rangle n = A,T,C or G
       <400> 96
 ctgaagcatt tcttcaaact intctactit tgtcattgat acctgtagta agttgacaat
gtggtgaaat ttcaaaatta tatgtaactt ctactagttt tactttctcc cccaagtctt
                                                                          60
ttttaactca tgatttttac acacacaatc cagaacttat tatatagcct ctaagtcttt
                                                                         120
attetteaca gtagatgatg aaagagteet ecagtgtett gngcanaatg ttetagntat
                                                                        180
agctggatac atacngtggg agttctataa actcatacct cagtgggact naaccaaaat
                                                                        240
tgtgttagtc tcaattccta ccacactgag ggagcctccc aaatcactat attcttatct
                                                                        300
gcaggtactc ctccagaaaa acngacaggg caggcttgca tgaaaaagtn acatctgcgt
                                                                        360
tacaaagtct atcttcctca nangtctgtn aaggaacaat ttaatcttct agcttt
                                                                        420
                                                                        476
      <210> 97
      <211> 479
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(479)
      <223> n = A, T, C or G
      <400> 97
actettteta atgetgatat gatettgagt ataagaatge atatgteact agaatggata
aaataatgct gcaaacttaa tgttcttatg caaaatggaa cgctaatgaa acacagctta
                                                                         60
                                                                        120
```

caatcgcaaa tcaaaactca gattgtgctc cttcggatat caggctacta gaattctgtt gtgattatna aattaatcac ntnnttttta natcaaagta ttcnatctta tttttcccn	gattgtttct attggatatn aaatttcact ttttgtgttt	canatcttgg tgagagcatg tatacctgct ggaantgtnn	gcaatnttcc aaatttttaa atcagcagct aaatgaaatc	ttagtcaaat naatacactt agaaaaacat tgaatgtggg	180 240 300 360 420 479
<210> 98 <211> 461 <212> DNA <213> Homo sapie	n				
<pre>&lt;400&gt; 98 agtgacttgt cctccaacaa tgctagttcc tgtcatctat tcaactccag ctggattatt agtgattcag tttcctctac tgaagccact ctgaacacgc ttacctggag aaaagaggct ttaagaaaaa ctaccacatg tttggaataa tcttgacgct</pre>	tcgctactaa ttggagcctg ggatgagaga tggttatcta ttggctgggg ttgtgtatcc	atgcagactg caaatctatt ctggctcaag gatgagaaca accatcccat tggtgccggc	gaggggacca cctacttgta aatatcctca gagaaataaa tgaaccttct cgtttatgaa	aaaaggggca cggactttga tgcagcttta gtcagaaaat cttaaggact	60 120 180 240 300 360 420 461
<210> 99 <211> 171 <212> DNA <213> Homo sapie	n				
<pre>&lt;400&gt; 99 gtggccgcgc gcaggtgttt c cggcgcctct gcgggcccga c cggtgagaaa agccttctct a &lt;210&gt; 100</pre>	ggaggagcgg	ctggcgggtg	gggggagtgt	gacccaccct	60 120 171
<211> 269 <212> DNA <213> Homo sapie	n				
<pre>&lt;400&gt; 100 cggccgcaag tgcaactcca g cgactgcgac gacggcggcg g aaggctgagc tgacgccgca g cagccggaac agagcccggt g cgagagatac gcaggtgcag g</pre>	gcgacagtcg gaggtcgtgt gaagcgggag	caggtgcagc cacgtcccac	gcgggcgcct gaccttgacg	ggggtcttgc ccgtcgggga	60 120 180 240 269
<210> 101 <211> 405 <212> DNA <213> Homo sapier	n				
<400> 101 ttttttttt ttttggaatc t gctagcaagg taacagggta g ttgattggtt tgtctttatg g agtgggtgca ccctccctgt a tgaccgtcat tttcttgaca t	gggcatggtt ggggcggggt agaacctggt	acatgttcag ggggtagggg tacaaagctt	gtcaacttcc aaacgaagca ggggcagttc	tttgtcgtgg aataacatgg acctggtctg	60 120 180 240 300

<212> DNA

ctgttctgga gggagattag ggtttcttgc caaatccaac aaaatccact gaaaaagttg gatgatcagt acgaataccg aggcatattc tcatatcggt ggcca	360
<210> 102	405
<211> 470	
<212> DNA	
<213> Homo sapien	
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The state of the s	360
	420
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GIZ	, Lys 50	3 Ar	g Sei	: Lei	ı Val	. Leı	ı Asp	) Let	ı Lys	Glı	n Pro	Arg	Gly	Ala	Ala	
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Arg	Arg	Gly	/ Val	Met		Lys	Leu	Glr	ı I.e.	75 . Gls	. Drie	. (1)		•	80 Gln	
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Arg	Glu	Asr	Pro	: Arg	Leu	Ile	Tyr	Ala	Arg	Leu	ı Ser	Gly	Phe	Glv	Gln	
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41

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	1260
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	1620
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	1860
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o so	1980
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	2280
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The substitute of the substitu	2460
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	2580
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The second continuous of the second continues of the s	2760
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	2880
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PCT/US99/15838

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260 265 Arg Leu Phe Val Ala Glu Leu Cys Ser Trp Met Ala Leu Met Thr Phe 280 285 Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu Gly Leu Tyr Gln Gly Val 295 300 Pro Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp Glu Gly 310 315 Val Arg Met Gly Ser Leu Gly Leu Phe Leu Gln Cys Ala Ile Ser Leu 325 330 Val Phe Ser Leu Val Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg 345 Ala Val Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala 360 Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu 375 Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr Leu Ala 390 395 Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro Lys Tyr Arg Gly 405 410 Asp Thr Gly Gly Ala Ser Ser Glu Asp Ser Leu Met Thr Ser Phe Leu 420 425 Pro Gly Pro Lys Pro Gly Ala Pro Phe Pro Asn Gly His Val Gly Ala 440 445 Gly Gly Ser Gly Leu Leu Pro Pro Pro Pro Ala Leu Cys Gly Ala Ser 455 460 Ala Cys Asp Val Ser Val Arg Val Val Gly Glu Pro Thr Glu Ala 470 475 Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile Leu Asp 485 490 Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met Gly Ser 500 505 Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met Val Ser Ala Ala 520 525 Gly Leu Gly Leu Val Ala Ile Tyr Phe Ala Thr Gln Val Val Phe Asp 535 Lys Ser Asp Leu Ala Lys Tyr Ser Ala 545 550 <210> 114 <211> 241 <212> PRT <213> Homo sapien <400> 114 Met Gln Cys Phe Ser Phe Ile Lys Thr Met Met Ile Leu Phe Asn Leu 10 Leu Ile Phe Leu Cys Gly Ala Ala Leu Leu Ala Val Gly Ile Trp Val 25 Ser Ile Asp Gly Ala Ser Phe Leu Lys Ile Phe Gly Pro Leu Ser Ser Ser Ala Met Gln Phe Val Asn Val Gly Tyr Phe Leu Ile Ala Ala Gly

55

70

Val Val Val Phe Ala Leu Gly Phe Leu Gly Cys Tyr Gly Ala Lys Thr

Glu Ser Lys Cys Ala Leu Val Thr Phe Phe Phe Ile Leu Leu Ile

75

```
85
                                      90
 Phe Ile Ala Glu Val Ala Ala Val Val Ala Leu Val Tyr Thr Thr
                                 105
                                                      110
 Met Ala Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys
                             120
                                                 125
 Asp Tyr Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met
                         135
                                             140
 Lys Gly Leu Lys Cys Cys Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp
                     150
                                         155
 Ser Pro Tyr Phe Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn
                 165
                                     170
 Asp Asn Val Thr Asn Thr Ala Asn Glu Thr Cys Thr Lys Gln Lys Ala
             180
                                 185
His Asp Gln Lys Val Glu Gly Cys Phe Asn Gln Leu Leu Tyr Asp Ile
                             200
Arg Thr Asn Ala Val Thr Val Gly Gly Val Ala Ala Gly Ile Gly Gly
                         215
                                             220
Leu Glu Leu Ala Ala Met Ile Val Ser Met Tyr Leu Tyr Cys Asn Leu
225
                     230
                                         235
Gln
      <210> 115
      <211> 366
      <212> DNA
      <213> Homo sapien
      <400> 115
gctctttctc tcccctcctc tgaatttaat tctttcaact tgcaatttgc aaggattaca
                                                                        60
catttcactg tgatgtatat tgtgttgcaa aaaaaaaaa gtgtctttgt ttaaaattac
                                                                       120
ttggtttgtg aatccatctt gctttttccc cattggaact agtcattaac ccatctctga
                                                                       180
actggtagaa aaacatctga agagctagtc tatcagcatc tgacaggtga attggatggt
                                                                       240
teteagaace attteaceea gacageetgt ttetateetg tttaataaat tagtttgggt
                                                                       300
tetetacatg cataacaaac cetgetecaa tetgteacat aaaagtetgt gaettgaagt
                                                                       360
ttagtc
                                                                       366
      <210> 116
      <211> 282
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(282)
      <223> n = A, T, C or G
      <400> 116
acaaagatga accatttcct atattatagc aaaattaaaa tctacccgta ttctaatatt
                                                                       60
gagaaatgag atnaaacaca atnttataaa gtctacttag agaagatcaa gtgacctcaa
agactttact attttcatat tttaagacac atgatttatc ctattttagt aacctggttc
                                                                      120
atacgttaaa caaaggataa tgtgaacagc agagaggatt tgttggcaga aaatctatgt
                                                                      180
                                                                      240
tcaatcinga actaictana tcacagacat tictaticci ti
                                                                      282
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<210> 117 <211> 305

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<212> DNA
       <213> Homo sapien
      <220>
       <221> misc_feature
      <222> (1)...(305)
      <223> n = A,T,C \text{ or } G
      <400> 117
acacatgtcg cttcactgcc ttcttagatg cttctggtca acatanagga acagggacca
                                                                          60
tatttatcct ccctcctgaa acaattgcaa aataanacaa aatatatgaa acaattgcaa
                                                                         120
aataaggcaa aatatatgaa acaacaggtc tcgagatatt ggaaatcagt caatgaagga
                                                                         180
tactgatccc tgatcactgt cctaatgcag gatgtgggaa acagatgagg tcacctctgt
                                                                         240
gactgcccca gcttactgcc tgtagagagt ttctangctg cagttcagac agggagaaat
                                                                         300
tgggt
                                                                         305
      <210> 118
      <211> 71
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(71)
      <223> n = A,T,C \text{ or } G
      <400> 118
accaaggtgt ntgaatctct gacgtgggga tctctgattc ccgcacaatc tgagtggaaa
                                                                          60
aantcctggg t
                                                                          71
      <210> 119
      <211> 212
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ...(212)
      <223> n = A, T, C \text{ or } G
      <400> 119
actccggttg gtgtcagcag cacgtggcat tgaacatngc aatgtggagc ccaaaccaca
                                                                         60
gaaaatgggg tgaaattggc caactttcta tnaacttatg ttggcaantt tgccaccaac
                                                                         120
agtaagctgg cccttctaat aaaagaaaat tgaaaggttt ctcactaanc ggaattaant
                                                                         180
aatggantca aganactccc aggcctcagc gt
                                                                         212
      <210> 120
      <211> 90
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (90)
      <223> n = A,T,C or G
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<pre>&lt;400&gt; 120 actcgttgca natcaggggc cccccagagt caccgttgca ggagtccttc tggtcttgcc ctccgccggc gcagaacatg ctggggtggt </pre>	60 90
<211> 218 <212> DNA <213> Homo sapien	
<220> <221> misc_feature <222> (1)(218) <223> n = A,T,C or G	
<400> 121	
tgtancgtga anacgacaga nagggttgtc aaaaatggag aanccttgaa gtcattttga gaataagatt tgctaaaaga tttggggcta aaacatggtt attgggg	60 120
atatnoangt aaattangga atgaattoat ggttottttg ggaattoott tacgatngco agoatanact toatgtgggg atanoagota coottgta	180
<210> 122	218
<210> 122 <211> 171	
<212> DNA	
<213> Homo sapien	
<400> 122	
taggggtgta tgcaactgta aggacaaaaa ttgagactca actggcttaa ccaataaagg	60
	60
caccaccccg gcggggtcat ctgtgccaca ggtccctgtt gacagtgcgg t	120 171
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<211> 76	
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<213> Homo sapien	
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<222> (1) (76)	
$\langle 223 \rangle$ n = A,T,C or G	
<400> 123	
tgtagcgtga agacnacaga atggtgtgtg ctgtgctatc caggaacaca tttattatca ttatcaanta ttgtgt	60 76
<210> 124	
<211> 131	
<212> DNA	
<213> Homo sapien	
<400> 124	
acctttcccc aaggccaatg tcctgtgtgc taactggccg gctgcaggac agctgcaatt	60
caatgtgctg ggtcatatgg aggggaggag actctaaaat agccaatttt attctcttgg	120
	131

WO 00/04149 PCT/US99/15838 · · · 49

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<210> 125
      <211> 432
      <212> DNA
      <213> Homo sapien
      <400> 125
actttatcta ctggctatga aatagatggt ggaaaattgc gttaccaact ataccactgg
                                                                        60
cttgaaaaag aggtgatagc tcttcagagg acttgtgact tttgctcaga tgctgaagaa
                                                                       120
ctacagtctg catttggcag aaatgaagat gaatttggat taaatgagga tgctgaagat
                                                                       180
ttgcctcacc aaacaaagt gaaacaactg agagaaaatt ttcaggaaaa aagacagtgg
                                                                       240
ctcttgaagt atcagtcact tttgagaatg tttcttagtt actgcatact tcatggatcc
                                                                       300
catggtgggg gtcttgcatc tgtaagaatg gaattgattt tgcttttgca agaatctcag
                                                                       360
caggaaacat cagaaccact attttctagc cctctgtcag agcaaacctc agtgcctctc
                                                                       420
ctctttgctt qt
                                                                       432
      <210> 126
      <211> 112
      <212> DNA
      <213> Homo sapien
      <400> 126
acacaacttg aatagtaaaa tagaaactga gctgaaattt ctaattcact ttctaaccat
                                                                        60
agtaagaatg atatttcccc ccagggatca ccaaatattt ataaaaattt gt
                                                                       112
      <210> 127
      <211> 54
      <212> DNA
      <213> Homo sapien
      <400> 127
accacgaaac cacaaacaag atggaagcat caatccactt gccaagcaca gcag
                                                                        54
    <210> 128
      <211> 323
      <212> DNA
      <213> Homo sapien
      <400> 128
acctcattag taattgtttt gttgtttcat ttttttctaa tgtctcccct ctaccagctc
                                                                        60
acctgagata acagaatgaa aatggaagga cagccagatt tctcctttgc tctctgctca
                                                                       120
ttctctctga agtctaggtt acccattttg gggacccatt ataggcaata aacacagttc
                                                                       180
ccaaagcatt tggacagttt cttgttgtgt tttagaatgg ttttcctttt tcttagcctt
                                                                       240
ttcctgcaaa aggctcactc agtcccttgc ttgctcagtg gactgggctc cccagggcct
                                                                       300
aggctgcctt cttttccatg tcc
                                                                       323
      <210> 129
      <211> 192
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(192)
      <223> n = A, T, C or G
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60

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<400> 129
 acatacatgt gtgtatattt ttaaatatca cttttgtatc actctgactt tttagcatac
 tgaaaacaca ctaacataat tintgigaac catgatcaga tacaacccaa atcattcatc
                                                                          60
 tagcacattc atctgtgata naaagatagg tgagtttcat ttccttcacg ttggccaatg
                                                                          120
                                                                         180
 gataaacaaa gt
                                                                         192
       <210> 130
       <211> 362
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(362)
       <223> n = A,T,C \text{ or } G
       <400> 130
ccctttttta tggaatgagt agactgtatg tttgaanatt tanccacaac ctctttgaca
tataatgacg caacaaaaag gtgctgttta gtcctatggt tcagtttatg cccctgacaa
                                                                          60
gtttccattg tgttttgccg atcttctggc taatcgtggt atcctccatg ttattagtaa
                                                                         120
ttctgtattc cattttgtta acgcctggta gatgtaacct gctangaggc taactttata
                                                                         180
cttatttaaa agctcttatt ttgtggtcat taaaatggca atttatgtgc agcactttat
                                                                         240
tgcagcagga agcacgtgtg ggttggttgt aaagctcttt gctaatctta aaaagtaatg
                                                                         300
                                                                         360
gg
                                                                        362
      <210> 131
      <211> 332
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (332)
      <223> n = A,T,C or G
      <400> 131
ctttttgaaa gatcgtgtcc actcctgtgg acatcttgtt ttaatggagt ttcccatgca
gtangactgg tatggttgca gctgtccaga taaaaacatt tgaagagctc caaaatgaga
                                                                         60
gttctcccag gttcgccctg ctgctccaag tctcagcagc agcctctttt aggaggcatc
                                                                        120
ttctgaacta gattaaggca gcttgtaaat ctgatgtgat ttggtttatt atccaactaa
                                                                        180
cttccatctg ttatcactgg agaaagccca gactccccan gacnggtacg gattgtgggc
                                                                        240
                                                                        300
atanaaggat tgggtgaagc tggcgttgtg gt
                                                                        332
      <210> 132
      <211> 322
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(322)
      <223> n = A, T, C \text{ or } G
     <400> 132
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actititgcca titigtatat ataaacaatc tigggacatt ciccigaaaa ciaggigicc

```
agtggctaag agaactcgat ttcaagcaat tctgaaagga aaaccagcat gacacagaat
                                                                         120
ctcaaattcc caaacagggg ctctgtggga aaaatgaggg aggacctttg tatctcgggt
                                                                         180
tttagcaagt taaaatgaan atgacaggaa aggcttattt atcaacaaag agaagagttg
                                                                         240
ggatgcttct aaaaaaaact ttggtagaga aaataggaat gctnaatcct agggaagcct
                                                                         300
gtaacaatct acaattggtc ca
                                                                         322
      <210> 133
      <211> 278
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(278)
      \langle 223 \rangle n = A,T,C or G
      <400> 133
acaagccttc acaagtttaa ctaaattggg attaatcttt ctgtanttat ctgcataatt
                                                                          60
cttgtttttc tttccatctg gctcctgggt tgacaatttg tggaaacaac tctattgcta
                                                                         120
ctatttaaaa aaaatcacaa atctttccct ttaagctatg ttnaattcaa actattcctg
                                                                         180
ctattcctgt tttgtcaaag aaattatatt tttcaaaata tgtntatttg tttgatgggt
                                                                         240
cccacgaaac actaataaaa accacagaga ccagcctg
                                                                        278
      <210> 134
      <211> 121
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(121)
      \langle 223 \rangle n = A,T,C or G
      <400> 134
gtttanaaaa cttgtttagc tccatagagg aaagaatgtt aaactttgta ttttaaaaca
                                                                         60
tgattctctg aggttaaact tggttttcaa atgttattt tacttgtatt ttgcttttgg
                                                                        120
                                                                        121
      <210> 135
      <211> 350
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(350)
      <223> n = A, T, C \text{ or } G
      <400> 135
acttanaacc atgcctagca catcagaatc cctcaaagaa catcagtata atcctatacc
                                                                         60
atancaagtg gtgactggtt aagcgtgcga caaaggtcag ctggcacatt acttgtgtgc
                                                                        120
aaacttgata cttttgttct aagtaggaac tagtatacag tncctaggan tggtactcca
                                                                        180
gggtgccccc caactcctgc agccgctcct ctgtgccagn ccctgnaagg aactttcgct
                                                                        240
ccacctcaat caagccctgg gccatgctac ctgcaattgg ctgaacaaac gtttgctgag
                                                                        300
ttcccaagga tgcaaagcct ggtgctcaac tcctggggcg tcaactcagt
                                                                        350
```

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<210> 136
        <211> 399
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc_feature
        <222> (1)...(399)
        \langle 223 \rangle n = A,T,C or G
        <400> 136
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 gctgtgattg tatccgaata ntcctcgtga gaaaagataa tgagatgacg tgagcagcct
                                                                           60
 gcagacttgt gtctgccttc aanaagccag acaggaaggc cctgcctgcc ttggctctga
                                                                           120
 cctggcggcc agccagccag ccacaggtgg gcttcttcct tttgtggtga caacnccaag
                                                                          180
 aaaactgcag aggcccaggg tcaggtgtna gtgggtangt gaccataaaa caccaggtgc
                                                                          240
 teccaggaac cegggeaaag gecateceea cetacageea geatgeecac tggegtgatg
                                                                          300
 ggtgcagang gatgaagcag ccagntgttc tgctgtggt
                                                                          360
                                                                          399
       <210> 137
       <211> 165
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(165)
       \langle 223 \rangle n = A,T,C or G
       <400> 137
actggtgtgg tngggggtga tgctggtggt anaagttgan gtgacttcan gatggtgtgt
ggaggaagtg tgtgaacgta gggatgtaga ngttttggcc gtgctaaatg agcttcggga
                                                                           60
ttggctggtc ccactggtgg tcactgtcat tggtggggtt cctgt
                                                                          120
                                                                          165
      <210> 138
      <211> 338
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(338)
      \langle 223 \rangle n = A,T,C or G
      <400> 138
actcactgga atgccacatt cacaacagaa tcagaggtct gtgaaaacat taatggctcc
ttaacttctc cagtaagaat cagggacttg aaatggaaac gttaacagcc acatgcccaa
                                                                          60
tgctgggcag tctcccatgc cttccacagt gaaaagggctt gagaaaaatc acatccaatg
                                                                         120
tcatgtgttt ccagccacac caaaaggtgc ttggggtgga gggctggggg catananggt
                                                                         180
cangeeteag gaageeteaa getecattea getetgeeae tgtacattee ceatnettaa
                                                                         240
aaaaactgat gcctttttt ttttttttt taaaattc
                                                                         300
                                                                         338
      <210> 139
      <211> 382
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<212> DNA
      <213> Homo sapien
      <400> 139
gggaatcttg gtttttggca tctggtttgc ctatagccga ggccactttg acagaacaaa
                                                                        60
gaaagggact tcgagtaaga aggtgattta cagccagcct agtgcccgaa gtgaaggaga
                                                                       120
attcaaacag acctcgtcat tcctggtgtg agcctggtcg gctcaccgcc tatcatctgc
                                                                       180
atttgcctta ctcaggtgct accggactct ggcccctgat gtctgtagtt tcacaggatg
                                                                       240
ccttatttgt cttctacacc ccacagggcc ccctacttct tcggatgtgt ttttaataat
                                                                       300
gtcagctatg tgccccatcc tccttcatgc cctccctccc tttcctacca ctgctgagtg
                                                                       360
gcctggaact tgtttaaagt gt
                                                                       382
      <210> 140
      <211> 200
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(200)
      \langle 223 \rangle n = A,T,C or G
      <400> 140
accaaanctt ctttctgttg tgttngattt tactataggg gtttngcttn ttctaaanat
                                                                        60
actiticati taacanciii tgitaagigi caggoigcac tiigciccat anaattatig
                                                                       120
ttttcacatt tcaacttgta tgtgtttgtc tcttanagca ttggtgaaat cacatatttt
                                                                       180
atattcagca taaaggagaa
                                                                       200
      <210> 141
      <211> 335
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(335)
      <223> n = A,T,C or G
      <400> 141
actttatttt caaaacactc atatgttgca aaaaacacat agaaaaataa agtttggtgg
                                                                        60
gggtgctgac taaacttcaa gtcacagact tttatgtgac agattggagc agggtttgtt
                                                                       120
atgcatgtag agaacccaaa ctaatttatt aaacaggata gaaacaggct gtctgggtga
                                                                       180
aatggttctg agaaccatcc aattcacctg tcagatgctg atanactagc tcttcagatg
                                                                       240
tttttctacc agttcagaga tnggttaatg actanttcca atggggaaaa agcaagatgg
                                                                       300
attcacaaac caagtaattt taaacaaaga cactt
                                                                       335
      <210> 142
      <211> 459
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(459)
      <223> n = A,T,C or G
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<400> 142
  accaggitaa tattgccaca tatatccttt ccaattgcgg gctaaacaga cgtgtattta
  gggttgttta aagacaaccc agcttaatat caagagaaat tgtgaccttt catggagtat
                                                                           60
  ctgatggaga aaacactgag ttttgacaaa tcttatttta ttcagatagc agtctgatca
                                                                          120
  cacatggtcc aacaacactc aaataataaa tcaaatatna tcagatgtta aagattggtc
                                                                          180
  ttcaaacatc atagccaatg atgccccgct tgcctataat ctctccgaca taaaaccaca
                                                                          240
  tcaacacctc agtggccacc aaaccattca gcacagcttc cttaactgtg agctgtttga
                                                                          300
 agctaccagt ctgagcacta ttgactatnt ttttcangct ctgaatagct ctagggatct
                                                                          360
                                                                          420
 cagcangggt gggaggaacc agctcaacct tggcgtant
                                                                         459
        <210> 143
        <211> 140
        <212> DNA
        <213> Homo sapien
       <400> 143
 acatttcctt ccaccaagtc aggactcctg gcttctgtgg gagttcttat cacctgaggg
 aaatccaaac agtctctcct agaaaggaat agtgtcacca accccaccca tctccctgag
                                                                          60
                                                                         120
 accatccgac ttccctgtgt
                                                                         140
       <210> 144
       <211> 164
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(164)
       <223> n = A,T,C \text{ or } G
       <400> 144
acttcagtaa caacatacaa taacaacatt aagtgtatat tgccatcttt gtcatttct
atctatacca ctctcccttc tgaaaacaan aatcactanc caatcactta tacaaatttg
                                                                         60
aggcaattaa tccatatttg ttttcaataa ggaaaaaaag atgt
                                                                        120
                                                                        164
       <210> 145
       <211> 303
       <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(303)
      \langle 223 \rangle n = A,T,C or G
      <400> 145
acgtagacca tccaactttg tatttgtaat ggcaaacatc cagnagcaat tcctaaacaa
actggagggt atttataccc aattatccca ttcattaaca tgccctcctc ctcaggctat
                                                                         60
gcaggacagc tatcataagt cggcccaggc atccagatac taccatttgt ataaacttca
                                                                        120
gtaggggagt ccatccaagt gacaggtcta atcaaaggag gaaatggaac ataagcccag
                                                                        180
tagtaaaatn ttgcttagct gaaacagcca caaaagactt accgccgtgg tgattaccat
                                                                        240
                                                                        300
caa
                                                                        303
```

```
<211> 327
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(327)
      \langle 223 \rangle n = A,T,C or G
      <400> 146
actgcagete aattagaagt ggtetetgae ttteateane tteteeetgg geteeatgae
                                                                         60
actggcctgg agtgactcat tgctctggtt ggttgagaga gctcctttgc caacaggcct
                                                                        120
ccaagtcagg gctgggattt gtttcctttc cacattctag caacaatatg ctggccactt
                                                                        180
cctgaacagg gagggtggga ggagccagca tggaacaagc tgccactttc taaagtagcc
                                                                        240
agacttgece etgggeetgt cacacetact gatgacette tgtgeetgea ggatggaatg
                                                                        300
taggggtgag ctgtgtgact ctatggt
                                                                        327
      <210> 147
      <211> 173
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(173)
      \langle 223 \rangle n = A,T,C or G
      <400> 147
acattgtttt tttgagataa agcattgana gagctctcct taacgtgaca caatggaagg
                                                                         60
actggaacac atacccacat ctttgttctg agggataatt ttctgataaa gtcttgctgt
                                                                        120
atattcaagc acatatgtta tatattattc agttccatgt ttatagccta gtt
                                                                        173
      <210> 148
      <211> 477
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(477)
      \langle 223 \rangle n = A,T,C or G
      <400> 148
acaaccactt tatctcatcg aatttttaac ccaaactcac tcactgtgcc tttctatcct
                                                                         60
atgggatata ttatttgatg ctccatttca tcacacatat atgaataata cactcatact
                                                                        120
gccctactac ctgctgcaat aatcacattc ccttcctgtc ctgaccctga agccattggg
                                                                        180
gtggtcctag tggccatcag tccangcctg caccttgagc ccttgagctc cattgctcac
                                                                        240
necaneceae eteaeegace ceatectett acaeagetae eteettgete tetaaeecea
                                                                        300
tagattatnt ccaaattcag tcaattaagt tactattaac actctacccg acatgtccag
                                                                        360
caccactggt aagccttctc cagccaacac acacacacac acacncacac acacacatat
                                                                        420
ccaggcacag gctacctcat cttcacaatc acccctttaa ttaccatgct atggtgg
                                                                        477
      <210> 149
      <211> 207
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<212> DNA

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<213> Homo sapien
        <400> 149
  acagttgtat tataatatca agaaataaac ttgcaatgag agcatttaag agggaagaac
  taacgtattt tagagagcca aggaaggttt ctgtggggag tgggatgtaa ggtggggcct
                                                                           60
  gatgataaat aagagtcagc caggtaagtg ggtggtgtgg tatgggcaca gtgaagaaca
                                                                          120
  tttcaggcag agggaacagc agtgaaa
                                                                          180
                                                                          207
        <210> 150
        <211> 111
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc_feature
       <222> (1) ... (111)
       <223> n = A,T,C \text{ or } G
       <400> 150
 accttgattt cattgctgct ctgatggaaa cccaactatc taatttagct aaaacatggg
 cacttaaatg tggtcagtgt ttggacttgt taactantgg catctttggg t
                                                                          60
                                                                         111
       <210> 151
       <211> 196
       <212> DNA
       <213> Homo sapien
       <400> 151
agcgcggcag gtcatattga acattccaga tacctatcat tactcgatgc tgttgataac
agcaagatgg ctttgaactc agggtcacca ccagctattg gaccttacta tgaaaaccat
                                                                          60
ggataccaac cggaaaaccc ctatcccgca cagcccactg tggtccccac tgtctacgag
                                                                         120
                                                                         180
 gtgcatccgg ctcagt
                                                                         196
       <210> 152
       <211> 132
       <212> DNA
      <213> Homo sapien
      <400> 152
acagcacttt cacatgtaag aagggagaaa ttcctaaatg taggagaaag ataacagaac
cttccccttt tcatctagtg gtggaaacct gatgctttat gttgacagga atagaaccag
                                                                         60
gagggagttt gt
                                                                        120
                                                                        132
      <210> 153
      <211> 285
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (285)
      <223> n = A,T,C \text{ or } G
      <400> 153
acaanaccca nganaggcca ctggccgtgg tgtcatggcc tccaaacatg aaagtgtcag
                                                                         60
```

```
cttctgctct tatgtcctca tctgacaact ctttaccatt tttatcctcg ctcagcagga
                                                                       120
gcacatcaat aaagtccaaa gtcttggact tggccttggc ttggaggaag tcatcaacac
                                                                       180
cctggctagt gagggtgcgg cgccgctcct ggatgacggc atctgtgaag tcgtgcacca
                                                                       240
gtctgcaggc cctgtggaag cgccgtccac acggagtnag qaatt
                                                                       285
      <210> 154
      <211> 333
      <212> DNA
      <213> Homo sapien
      <400> 154
accacagtcc tgttgggcca gggcttcatg accctttctg tgaaaagcca tattatcacc
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accccaaatt tttccttaaa tatctttaac tgaaggggtc agcctcttga ctgcaaagac
                                                                       120
cctaagccgg ttacacagct aactcccact ggccctgatt tgtgaaattg ctgctgcctg
                                                                       180
attggcacag gagtcgaagg tgttcagctc ccctcctccg tggaacgaga ctctgatttg
                                                                       240
agtttcacaa attctcgggc cacctcgtca ttgctcctct gaaataaaat ccggagaatg
                                                                       300
gtcaggcctg tctcatccat atggatcttc cgg
                                                                      333
      <210> 155
      <211> 308
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(308)
      <223> n = A.T.C or G
      <400> 155
actggaaata ataaaaccca catcacagtg ttgtgtcaaa gatcatcagg gcatggatgg
                                                                       60
gaaagtgctt tgggaactgt aaagtgccta acacatgatc gatgattttt gttataatat
                                                                      120
ttgaatcacg gtgcatacaa actctcctgc ctgctcctcc tgggccccag ccccagcccc
                                                                      180
atcacagete actgetetgt teatecagge ceageatgta gtggetgatt ettettgget
                                                                      240
gcttttagcc tccanaagtt tctctgaagc caaccaaacc tctangtgta aggcatgctg
                                                                      300
gccctggt
                                                                      308
      <210> 156
      <211> 295
      <212> DNA
      <213> Homo sapien
      <400> 156
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                                                                       60
ttattgatta ctgagagaac tgttagacat ttagttgaag attttctaca caggaactga
                                                                      120
gaataggaga ttatgtttgg ccctcatatt ctctcctatc ctccttgcct cattctatgt
                                                                      180
ctaatatatt ctcaatcaaa taaggttagc ataatcagga aatcgaccaa ataccaatat
                                                                      240
aaaaccagat gtctatcctt aagattttca aatagaaaac aaattaacag actat
                                                                      295
      <210> 157
      <211> 126
      <212> DNA
      <213> Homo sapien
      <400> 157
acaagtttaa atagtgctgt cactgtgcat gtgctgaaat gtgaaatcca ccacatttct
                                                                       60
```

```
gaagagcaaa acaaattctg tcatgtaatc tctatcttgg gtcgtgggta tatctgtccc
                                                                          120
 cttagt
                                                                          126
       <210> 158
       <211> 442
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(442)
       \langle 223 \rangle n = A,T,C or G
       <400> 158
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aanccagcag gctgccccta gtcagtcctt ccttccagag aaaaagagat ttgagaaagt
                                                                           60
gcctgggtaa ttcaccatta atttcctccc ccaaactctc tgagtcttcc cttaatattt
                                                                         120
ctggtggttc tgaccaaagc aggtcatggt ttgttgagca tttggggatcc cagtgaagta
                                                                         180
natgtttgta gccttgcata cttagccctt cccacgcaca aacggagtgg cagagtggtg
                                                                         240
ccaaccetgt tttcccagte caegtagaca gattcacagt geggaattet ggaagetgga
                                                                         300
nacagacggg ctctttgcag agccgggact ctgagangga catgagggcc tctgcctctg
                                                                         360
                                                                         420
tgttcattct ctgatgtcct gt
                                                                         442
      <210> 159
      <211> 498
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(498)
      <223> n = A,T,C \text{ or } G
      <400> 159
acttccaggt aacgttgttg tttccgttga gcctgaactg atgggtgacg ttgtaggttc
tccaacaaga actgaggttg cagagcgggt agggaagagt gctgttccag ttgcacctgg
                                                                         60
gctgctgtgg actgttgttg attcctcact acggcccaag gttgtggaac tggcanaaag
                                                                        120
gtgtgttgtt gganttgagc tcgggcggct gtggtaggtt gtgggctctt caacaggggc
                                                                        180
tgctgtggtg ccgggangtg aangtgttgt gtcacttgag cttggccagc tctggaaagt
                                                                        240
antanattct tcctgaaggc cagcgcttgt ggagctggca ngggtcantg ttgtgtgtaa
                                                                        300
cgaaccagtg ctgctgtggg tgggtgtana tcctccacaa agcctgaagt tatggtgtcn
                                                                        360
tcaggtaana atgtggtttc agtgtccctg ggcngctgtg gaaggttgta nattgtcacc
                                                                        420
                                                                        480
aagggaataa gctgtggt
                                                                        498
      <210> 160
      <211> 380
      <212> DNA
      <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1) ... (380)
     \langle 223 \rangle n = A,T,C or G
     <400> 160
```

WO 00/04149 PCT/US99/15838 59

```
acctgcatcc agcttccctg ccaaactcac aaggagacat caacctctag acagggaaac
                                                                        60
agetteagga taetteeagg agacagagee accageagea aaacaaatat teecatgeet
                                                                        120
ggagcatggc atagaggaag ctganaaatg tggggtctga ggaagccatt tgagtctggc
                                                                        180
cactagacat ctcatcagcc acttgtgtga agagatgccc catgacccca gatgcctctc
                                                                        240
ccaccettac etccatetca cacacttgag etttecaete tgtataatte taacateetg
                                                                        300
gagaaaaatg gcagtttgac cgaacctgtt cacaacggta gaggctgatt tctaacgaaa
                                                                        360
cttgtagaat gaagcctgga
                                                                        380
      <210> 161
      <211> 114
      <212> DNA
      <213> Homo sapien
      <400> 161
actccacatc ccctctgagc aggcggttgt cgttcaaggt gtatttggcc ttgcctgtca
                                                                        60
cactgtccac tggcccctta tccacttggt gcttaatccc tcgaaagagc atgt
                                                                        114
      <210> 162
      <211> 177
      <212> DNA
      <213> Homo sapien
      <400> 162
actttctgaa tcgaatcaaa tgatacttag tgtagtttta atatcctcat atatatcaaa
                                                                        60
gttttactac tctgataatt ttgtaaacca ggtaaccaga acatccagtc atacagcttt
                                                                       120
tggtgatata taacttggca ataacccagt ctggtgatac ataaaactac tcactgt
                                                                       177
      <210> 163
      <211> 137
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(137)
      <223> n = A, T, C \text{ or } G
      <400> 163
catttataca gacaggcgtg aagacattca cgacaaaaac gcgaaattct atcccgtgac
                                                                        60
canagaaggc agctacggct actcctacat cctggcgtgg gtggccttcg cctgcacctt
                                                                       120
catcagcggc atgatgt
                                                                       137
      <210> 164
      <211> 469
      <212> DNA
     <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(469)
      \langle 223 \rangle n = A,T,C or G
      <400> 164
cttatcacaa tgaatgttct cctgggcagc gttgtgatct ttgccacctt cgtgacttta
                                                                        60
tgcaatgcat catgctattt catacctaat gagggagttc caggagattc aaccaggaaa
                                                                       120
```

```
tgcatggatc tcaaaggaaa caaacaccca ataaactcgg agtggcagac tgacaactgt
 gagacatgca cttgctacga aacagaaatt tcatgttgca cccttgtttc tacacctgtg
                                                                          180
 ggttatgaca aagacaactg ccaaagaatc ttcaagaagg aggactgcaa gtatatcgtg
                                                                          240
 gtggagaaga aggacccaaa aaagacctgt tctgtcagtg aatggataat ctaatgtgct
                                                                          300
 totagtaggc acagggctcc caggccaggc ctcattctcc tctggcctct aatagtcaat
                                                                          360
 gattgtgtag ccatgcctat cagtaaaaag atntttgagc aaacacttt
                                                                          420
                                                                          469
        <210> 165
       <211> 195
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(195)
       <223> n = A,T,C or G
       <400> 165
 acagtttttt atanatatcg acattgccgg cacttgtgtt cagtttcata aagctggtgg
 atccgctgtc atccactatt ccttggctag agtaaaaatt attcttatag cccatgtccc
                                                                          60
 tgcaggccgc ccgcccgtag ttctcgttcc agtcgtcttg gcacacaggg tgccaggact
                                                                         120
                                                                         180
 tcctctgaga tgagt
                                                                         195
       <210> 166
       <211> 383
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(383)
       \langle 223 \rangle n = A,T,C or G
       <400> 166
acatcttagt agtgtggcac atcaggggc catcagggtc acagtcactc atagcctcgc
cgaggtcgga gtccacacca ccggtgtagg tgtgctcaat cttgggcttg gcgcccacct
                                                                          60
ttggagaagg gatatgctgc acacacatgt ccacaaagcc tgtgaactcg ccaaagaatt
                                                                        120
tttgcagacc agcctgagca aggggcggat gttcagcttc agctcctcct tcgtcaggtg
                                                                        180
gatgccaacc tcgtctangg tccgtgggaa gctggtgtcc acntcaccta caacctgggc
                                                                        240
gangatetta taaagagget eenagataaa eteeacgaaa ettetetggg agetgetagt
                                                                        300
                                                                        360
nggggccttt ttggtgaact ttc
                                                                        383
      <210> 167
      <211> 247
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(247)
      \langle 223 \rangle n \approx A,T,C or G
      <400> 167
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tggagcagaa actggagcaa gaagtgggcc tggggctgaa gtagagacca aggccactgc
                                                                        60
                                                                        120
```

```
tatanccata cacagageca acteteagge caaggenatg gttggggcag anccagagae
                                                                         180
tcaatctgan tccaaagtgg tggctggaac actggtcatg acanaggcag tgactctgac
                                                                         240
tgangtc
                                                                         247
      <210> 168
      <211> 273
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(273)
      \langle 223 \rangle n = A.T.C or G
      <400> 168
acttctaagt tttctagaag tggaaggatt gtantcatcc tgaaaatggg tttacttcaa
                                                                          60
aatccctcan ccttgttctt cacnactgtc tatactgana gtgtcatgtt tccacaaagg
                                                                         120
gctgacacct gagcctgnat tttcactcat ccctgagaag ccctttccag tagggtgggc
                                                                         180
aattcccaac ttccttgcca caagcttccc aggctttctc ccctggaaaa ctccagcttg
                                                                         240
agtcccagat acactcatgg gctgccctgg gca
                                                                         273
      <210> 169
      <211> 431
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(431)
      \langle 223 \rangle n = A,T,C or G
      <400> 169
acageettgg ettecceaaa etccaeagte teagtgeaga aagateatet tecageagte
                                                                          60
agctcagacc agggtcaaag gatgtgacat caacagtttc tggtttcaga acaggttcta
                                                                         120
ctactgtcaa atgacccccc atacttcctc aaaggctgtg gtaagttttg cacaggtgag
                                                                         180
ggcagcagaa agggggtant tactgatgga caccatcttc tctgtatact ccacactgac
                                                                         240
cttgccatgg gcaaaggccc ctaccacaaa aacaatagga tcactgctgg gcaccagctc
                                                                         300
acgcacatca ctgacaaccg ggatggaaaa agaantgcca actttcatac atccaactgg
                                                                         360
aaagtgatet gataetggat tettaattae etteaaaage ttetggggge cateagetge
                                                                         420
tcgaacactg a
                                                                         431
      <210> 170
      <211> 266
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(266)
      \langle 223 \rangle n = A,T,C or G
      <400> 170
acctgtgggc tgggctgtta tgcctgtgcc ggctgctgaa agggagttca gaggtggagc
                                                                         60
tcaaggagct ctgcaggcat tttgccaanc ctctccanag canagggagc aacctacact
                                                                         120
ccccgctaga aagacaccag attggagtcc tgggaggggg agttggggtg ggcatttgat
                                                                         180
```

```
gtatacttgt cacctgaatg aangagccag agaggaanga gacgaanatg anattggcct
                                                                         240
  tcaaagctag gggtctggca ggtgga
                                                                         266
        <210> 171
        <211> 1248
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc_feature
        <222> (1) ... (1248)
       \langle 223 \rangle n = A,T,C or G
       <400> 171
 ggcagccaaa tcataaacgg cgaggactgc agcccgcact cgcagccctg gcaggcggca
 ctggtcatgg aaaacgaatt gttctgctcg ggcgtcctgg tgcatccgca gtgggtgctg
                                                                         60
 tcagccgcac actgtttcca gaagtgagtg cagagctcct acaccatcgg gctgggcctg
                                                                        120
 cacagtettg aggeegaeea agageeaggg ageeagatgg tggaggeeag ceteteegta
                                                                        180
 cggcacccag agtacaacag accettgete getaacgace teatgeteat caagttggae
                                                                        240
 gaatccgtgt ccgagtctga caccatccgg agcatcagca ttgcttcgca gtgccctacc
                                                                        300
 gcggggaact cttgcctcgt ttctggctgg ggtctgctgg cgaacggcag aatgcctacc
                                                                        360
 gtgctgcagt gcgtgaacgt gtcggtggtg tctgaggagg tctgcagtaa gctctatgac
                                                                        420
 ccgctgtacc accccagcat gttctgcgcc ggcggagggc aagaccagaa ggactcctgc
                                                                        480
 aacggtgact ctggggggcc cctgatctgc aacgggtact tgcagggcct tgtgtctttc
                                                                        540
 ggaaaagccc cgtgtggcca agttggcgtg ccaggtgtct acaccaacct ctgcaaattc
                                                                        600
 actgagtgga tagagaaaac cgtccaggcc agttaactct ggggactggg aacccatgaa
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 attgacccc aaatacatcc tgcggaagga attcaggaat atctgttccc agcccctcct
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ccctcaggcc caggagtcca ggccccagc ccctcctccc tcaaaccaag ggtacagatc
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cccagcccct cctccctcag acccaggagt ccagaccccc cagcccctcc tccctcagac
                                                                        840
ccaggagtec agecectect ceetcagace caggagteca gaccecccag eccetectee
                                                                        900
ctcagaccca ggggtccagg cccccaaccc ctcctccctc agactcagag gtccaagcc
                                                                        960
ccaaccente attecceaga cccagaggte caggteccag eccetentee etcagaccea
                                                                       1020
geggtecaat gecaectaga ethteeetgt acaeagtgee eeettgtgge acgttgaece
                                                                       1080
aaccttacca gttggttttt catttttngt ccctttcccc tagatccaga aataaagttt
                                                                      1140
aagagaagng caaaaaaaaa aaaaaaaaa aaaaaaaa
                                                                      1200
                                                                      1248
       <210> 172
      <211> 159
      <212> PRT
      <213> Homo sapien
      <220>
      <221> VARIANT
      <222> (1)...(159)
      <223> Xaa = Any Amino Acid
      <400> 172
Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro
                 5
                                    10
Leu Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser
                                                        15
            20
                                25
Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr
                            40
Ala Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly
                                                45
    50
                        55
```

<222> (1)...(1459)

```
Arg Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu
                    70
                                         75
Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe
                85
                                    90
Cys Ala Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser
                                105
Gly Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe
        115
                            120
                                                125
Gly Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn
                        135
                                             140
Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
145
                    150
                                        155
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      <211> 1265
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(1265)
      \langle 223 \rangle n = A,T,C or G
      <400> 173
ggcagcccgc actcgcagcc ctggcaggcg gcactggtca tggaaaacga attgttctgc
                                                                        60
tegggegtee tggtgeatee geagtgggtg etgteageeg cacactgttt ceagaactee
                                                                       120
tacaccateg ggetgggeet geacagtett gaggeegace aagageeagg gageeagatg
                                                                       180
gtggaggcca gcctctccgt acggcaccca gagtacaaca gacccttgct cgctaacgac
                                                                       240
ctcatgctca tcaagttgga cgaatccgtg tccgagtctg acaccatccg gagcatcagc
                                                                       300
attgcttcgc agtgccctac cgcggggaac tcttgcctcg tttctggctg gggtctgctg
                                                                       360
gcgaacggtg agctcacggg tgtgtgtctg ccctcttcaa ggaggtcctc tgcccaqtcq
                                                                       420
cgggggctga cccagagete tgcgtcccag gcagaatgcc taccgtgctg cagtgcgtga
                                                                       480
acgtgtcggt ggtgtctgag gaggtctgca gtaagctcta tgacccgctg taccacccca
                                                                       540
gcatgttctg cgccggcgga gggcaagacc agaaggactc ctgcaacggt gactctgggg
                                                                       600
ggcccctgat ctgcaacggg tacttgcagg gccttgtgtc tttcggaaaa gccccqtqtq
                                                                       660
gccaagttgg cgtgccaggt gtctacacca acctctgcaa attcactgag tggatagaga
                                                                       720
aaaccgtcca ggccagttaa ctctggggac tgggaaccca tgaaattgac ccccaaatac
                                                                       780
atcctgcgga aggaattcag gaatatctgt tcccagcccc tcctccctca ggcccaggag
                                                                       840
tecaggeece cageecetee teceteaaac caagggtaca gateeceage ceeteetee
                                                                       900
tcagacccag gagtccagac cccccagccc ctcctccctc agacccagga gtccagcccc
                                                                       960
tecteentea gacceaggag tecagaceee ecageceete eteceteaga eccaggggtt
                                                                      1020
gaggccccca acccctcctc cttcagagtc agaggtccaa gcccccaacc cctcgttccc
                                                                      1080
cagacccaga ggtnnaggtc ccagcccctc ttccntcaga cccagnggtc caatgccacc
                                                                      1140
tagattttcc ctgnacacag tgcccccttg tggnangttg acccaacctt accagttqqt
                                                                      1200
ttttcatttt tngtcccttt cccctagatc cagaaataaa gtttaagaga ngngcaaaaa
                                                                      1260
aaaaa
                                                                      1265
      <210> 174
      <211> 1459
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
```

```
<223> n = A,T,C or G
```

```
<400> 174
 ggtcagccgc acactgtttc cagaagtgag tgcagagctc ctacaccatc gggctgggcc
 tgcacagtet tgaggeegae caagageeag ggageeagat ggtggaggee ageeteteeg
                                                                          60
 tacggcaccc agagtacaac agacccttgc tcgctaacga cctcatgctc atcaagttgg
                                                                         120
 acgaatccgt gtccgagtct gacaccatcc ggagcatcag cattgcttcg cagtgcccta
                                                                         180
 ccgcggggaa ctcttgcctc gtttctggct ggggtctgct ggcgaacggt gagctcacgg
                                                                         240
 gtgtgtgtct gccctcttca aggaggtcct ctgcccagtc gcgggggctg acccagagct
                                                                         300
 ctgcgtccca ggcagaatgc ctaccgtgct gcagtgcgtg aacgtgtcgg tggtgtctga
                                                                         360
 ngaggtetge antaagetet atgaceeget gtaceaeece ancatgttet gegeeggegg
                                                                         420
 agggcaagac cagaaggact cctgcaacgt gagagagggg aaaggggagg gcaggcgact
                                                                         480
 cagggaaggg tggagaaggg ggagacagag acacacaggg ccgcatggcg agatgcagag
                                                                        540
 atggagagac acacagggag acagtgacaa ctagagagag aaactgagag aaacagagaa
                                                                        600
 ataaacacag gaataaagag aagcaaagga agagagaaac agaaacagac atggggaggc
                                                                        660
 agaaacacac acacatagaa atgcagttga ccttccaaca gcatggggcc tgagggcggt
                                                                        720
 gacctccacc caatagaaaa tcctcttata acttttgact ccccaaaaac ctgactagaa
                                                                        780
 atagcctact gttgacgggg agccttacca ataacataaa tagtcgattt atgcatacgt
                                                                        840
 tttatgcatt catgatatac ctttgttgga attttttgat atttctaagc tacacagttc
                                                                        900
 gtctgtgaat ttttttaaat tgttgcaact ctcctaaaat ttttctgatg tgtttattga
                                                                        960
 aaaaatccaa gtataagtgg acttgtgcat tcaaaccagg gttgttcaag ggtcaactgt
                                                                       1020
 gtacccagag ggaaacagtg acacagattc atagaggtga aacacgaaga gaaacaggaa
                                                                       1080
 aaatcaagac tctacaaaga ggctgggcag ggtggctcat gcctgtaatc ccagcacttt
                                                                       1140
 gggaggcgag gcaggcagat cacttgaggt aaggagttca agaccagcct ggccaaaatg
                                                                       1200
 gtgaaateet gtetgtaeta aaaatacaaa agttagetgg atatggtgge aggegeetgt
                                                                       1260
 aatcccagct acttgggagg ctgaggcagg agaattgctt gaatatggga ggcagaggtt
                                                                       1320
gaagtgagtt gagatcacac cactatactc cagctggggc aacagagtaa gactctgtct
                                                                       1380
 caaaaaaaaa aaaaaaaaa
                                                                       1440
                                                                       1459
       <210> 175
       <211> 1167
       <212> DNA
       <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (1167)
      <223> n = A, T, C \text{ or } G
      <400> 175
gcgcagccct ggcaggcggc actggtcatg gaaaacgaat tgttctgctc gggcgtcctg
gtgcatccgc agtgggtgct gtcagccgca cactgtttcc agaactccta caccatcggg
                                                                        60
ctgggcctgc acagtcttga ggccgaccaa gagccaggga gccagatggt ggaggccagc
                                                                       120
ctctccgtac ggcacccaga gtacaacaga ctcttgctcg ctaacgacct catgctcatc
                                                                       180
aagttggacg aatccgtgtc cgagtctgac accatccgga gcatcagcat tgcttcgcag
                                                                       240
tgccctaccg cggggaactc ttgcctcgtn tctggctggg gtctgctggc gaacggcaga
                                                                       300
atgcctaccg tgctgcactg cgtgaacgtg tcggtggtgt ctgaggangt ctgcagtaag
                                                                       360
ctctatgacc cgctgtacca ccccagcatg ttctgcgccg gcggagggca agaccagaag
                                                                       420
gacteetgea aeggtgaete tggggggeee etgatetgea aegggtaett geagggeett
                                                                       480
gtgtctttcg gaaaagcccc gtgtggccaa cttggcgtgc caggtgtcta caccaacctc
                                                                       540
tgcaaattca ctgagtggat agagaaaacc gtccagncca gttaactctg gggactggga
                                                                       600
acccatgaaa ttgaccccca aatacatcct gcggaangaa ttcaggaata tctgttccca
                                                                       660
geceeteete eeteaggeee aggagteeag geceecagee eeteeteet caaaceaagg
                                                                       720
gtacagatec ecageceete eteceteaga eccaggagte cagaceceec ageceetent
                                                                       780
centeagace caggagteca geceetecte enteagacge aggagtecag acceeceage
                                                                       840
```

```
cententeeg teagaceeag gggtgeagge ecceaacece tenteentea gagteagagg
                                                                       960
tccaagcccc caacccctcg ttccccagac ccagaggtnc aggtcccagc ccctcctccc
                                                                     1020
tcagacccag cggtccaatg ccacctagan tntccctgta cacagtgccc ccttgtggca
                                                                     1080
ngttgaccca accttaccag ttggtttttc attttttgtc cctttcccct agatccagaa
                                                                     1140
ataaagtnta agagaagcgc aaaaaaa
                                                                     1167
      <210> 176
      <211> 205
      <212> PRT
      <213> Homo sapien
      <220>
      <221> VARIANT
      <222> (1) ... (205)
      <223> Xaa = Any Amino Acid
      <400> 176
Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp
                                    10
Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu
                                25
Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
                            40
Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Leu Leu
                        55
Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
                    70
                                        75
Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
                85
                                    90
Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met
            100
                                105
Pro Thr Val Leu His Cys Val Asn Val Ser Val Val Ser Glu Xaa Val
                            120
Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala
                                            140
Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly
                    150
                                        155
Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys
                                    170
Ala Pro Cys Gly Gln Leu Gly Val Pro Gly Val Tyr Thr Asn Leu Cys
                                185
Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Xaa Ser
      <210> 177
      <211> 1119
      <212> DNA
      <213> Homo sapien
      <400> 177
gcgcactcgc agccctggca ggcggcactg gtcatggaaa acgaattgtt ctgctcgggc
                                                                       60
gtcctggtgc atccgcagtg ggtgctgtca gccgcacact gtttccagaa ctcctacacc
                                                                      120
atcgggctgg gcctgcacag tcttgaggcc gaccaagagc cagggagcca gatggtggag
                                                                      180
gccagcctct ccgtacggca cccagagtac aacagaccct tgctcgctaa cgacctcatg
                                                                      240
ctcatcaagt tggacgaatc cgtgtccgag tctgacacca tccggagcat caqcattgct
                                                                      300
```

420

480

540

600

660

720

780

840

900

960

1020

1080 1119

```
tcgcagtgcc ctaccgcggg gaactcttgc ctcgtttctg gctggggtct gctggcgaac
 gatgctgtga ttgccatcca gtcccagact gtgggaggct gggagtgtga gaagctttcc
 caaccetgge agggttgtac cattteggea acttecagtg caaggaegte etgetgeate
 ctcactgggt gctcactact gctcactgca tcacccggaa cactgtgatc aactagccag
 caccatagtt ctccgaagtc agactatcat gattactgtg ttgactgtgc tgtctattgt
 actaaccatg ccgatgttta ggtgaaatta gcgtcacttg gcctcaacca tcttggtatc
 cagttatect caetgaattg agattteetg etteagtgte agecatteee acataattte
 tgacctacag aggtgaggga tcatatagct cttcaaggat gctggtactc ccctcacaaa
 ttcatttctc ctgttgtagt gaaaggtgcg ccctctggag cctcccaggg tgggtgtgca
 ggtcacaatg atgaatgtat gatcgtgttc ccattaccca aagcctttaa atccctcatg
 ctcagtacac cagggcaggt ctagcatttc ttcatttagt gtatgctgtc cattcatgca
 accacctcag gactcctgga ttctctgcct agttgagctc ctgcatgctg cctccttggg
 gaggtgaggg agagggccca tggttcaatg ggatctgtgc agttgtaaca cattaggtgc
 ttaataaaca gaagctgtga tgttaaaaaa aaaaaaaaa
       <210> 178
       <211> 164
       <212> PRT
       <213> Homo sapien
       <220>
       <221> VARIANT
      <222> (1)...(164)
      <223> Xaa = Any Amino Acid
      <400> 178
Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp
                5
                                   10
Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu
                                25
Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu
Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
                                        75
Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Asp Ala Val
                                105
Ile Ala Ile Gln Ser Xaa Thr Val Gly Gly Trp Glu Cys Glu Lys Leu
                            120
                                                125
Ser Gln Pro Trp Gln Gly Cys Thr Ile Ser Ala Thr Ser Ser Ala Arg
                       135
                                            140
Thr Ser Cys Cys Ile Leu Thr Gly Cys Ser Leu Leu Leu Thr Ala Ser
                   150
                                        155
                                                            160
Pro Gly Thr Leu
```

<210> 179

<211> 250

<212> DNA

<213> Homo sapien

<400> 179

```
ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct
                                                                        60
ccagetgeec ceggeegggg gatgegagge teggageace ettgeeegge tgtgattget
                                                                        120
gccaggcact gttcatctca gcttttctgt ccctttgctc ccggcaagcg cttctgctga
                                                                        180
aagttcatat ctggagcctg atgtcttaac gaataaaggt cccatgctcc acccgaaaaa
                                                                        240
aaaaaaaaa
                                                                        250
      <210> 180
      <211> 202
      <212> DNA
      <213> Homo sapien
      <400> 180
actagtccag tgtggtggaa ttccattgtg ttgggcccaa cacaatggct acctttaaca
                                                                        60
traccragar receptored acceptored acceptored taacgarage atgatecta
                                                                       120
ctctgctact cggaaactat ttttatgtaa ttaatgtatg ctttcttgtt tataaatgcc
                                                                       180
tgatttaaaa aaaaaaaaaa aa
                                                                       202
      <210> 181
      <211> 558
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(558)
      \langle 223 \rangle n = A,T,C or G
      <400> 181
tccytttgkt naggtttkkg agacamccck agacctwaan ctgtgtcaca gacttcyngg
                                                                        60
aatgtttagg cagtgctagt aatttcytcg taatgattct gttattactt tcctnattct
                                                                       120
ttattcctct ttcttctgaa gattaatgaa gttgaaaatt gaggtggata aatacaaaaa
                                                                       180
ggtagtgtga tagtataagt atctaagtgc agatgaaagt gtgttatata tatccattca
                                                                       240
aaattatgca agttagtaat tactcagggt taactaaatt actttaatat gctgttgaac
                                                                       300
ctactctgtt ccttggctag aaaaaattat aaacaggact ttgttagttt gggaagccaa
                                                                       360
attgataata ttctatgttc taaaagttgg gctatacata aattattaaq aaatatggaw
                                                                       420
ttttattccc aggaatatgg kgttcatttt atgaatatta cscrggatag awgtwtgagt
                                                                       480
aaaaycagtt ttggtwaata ygtwaatatg tcmtaaataa acaakgcttt gacttatttc
                                                                       540
caaaaaaaa aaaaaaaa
                                                                       558
      <210> 182
      <211> 479
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(479)
      \langle 223 \rangle n = A,T,C or G
      <400> 182
acagggwttk grggatgcta agsccccrga rwtygtttga tccaaccctg gcttwttttc
                                                                        60
agaggggaaa atggggccta gaagttacag mscatytagy tggtgcgmtg gcacccctqq
                                                                       120
cstcacacag astcccgagt agctgggact acaggcacac agtcactgaa gcaggccctg
                                                                       180
ttwgcaattc acgttgccac ctccaactta aacattcttc atatgtgatg tccttagtca
                                                                       240
ctaaggttaa actttcccac ccagaaaagg caacttagat aaaatcttag agtactttca
                                                                       300
```

```
tactmttcta agtcctcttc cagcctcact kkgagtcctm cytgggggtt gataggaant
  ntctcttggc tttctcaata aartctctat ycatctcatg tttaatttgg tacgcatara
                                                                         360
  awtgstgara aaattaaaat gttctggtty mactttaaaa araaaaaaaa aaaaaaaaa
                                                                         420
                                                                         479
        <210> 183
        <211> 384
        <212> DNA
        <213> Homo sapien
        <400> 183
 aggcgggagc agaagctaaa gccaaagccc aagaagagtg gcagtgccag cactggtgcc
 agtaccagta ccaataacag tgccagtgcc agtgccagca ccagtggtgg cttcagtgct
                                                                          60
 ggtgccagcc tgaccgccac tctcacattt gggctcttcg ctggccttgg tggagctggt
                                                                         120
 gccagcacca gtggcagctc tggtgcctgt ggtttctcct acaagtgaga ttttagatat
                                                                         180
 tgttaatcct gccagtcttt ctcttcaagc cagggtgcat cctcagaaac ctactcaaca
                                                                         240
 cagcactcta ggcagccact atcaatcaat tgaagttgac actctgcatt aratctattt
                                                                         300
                                                                         360
 gccatttcaa aaaaaaaaaa aaaa
                                                                         384
       <210> 184
       <211> 496
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(496)
       \langle 223 \rangle n = A,T,C or G
       <400> 184
accgaattgg gaccgctggc ttataagcga tcatgtyynt ccrgtatkac ctcaacgagc
agggagatcg agtctatacg ctgaagaaat ttgacccgat gggacaacag acctgctcag
                                                                         60
cccatcctgc tcggttctcc ccagatgaca aatactctsg acaccgaatc accatcaaga
                                                                        120
aacgetteaa ggtgeteatg acceageaac egegeeetgt cetetgaggg teeettaaac
                                                                        180
tgatgtcttt tctgccacct gttacccctc ggagactccg taaccaaact cttcggactg
                                                                        240
tgagccctga tgcctttttg ccagccatac tctttggcat ccagtctctc gtggcgattg
                                                                        300
attatgcttg tgtgaggcaa tcatggtggc atcacccata aagggaacac atttgacttt
                                                                        360
tttttctcat attttaaatt actacmagaw tattwmagaw waaatgawtt gaaaaactst
                                                                        420
taaaaaaaaa aaaaaa
                                                                        480
                                                                        496
      <210> 185
      <211> 384
      <212> DNA
      <213> Homo sapien
      <400> 185
gctggtagcc tatggcgkgg cccacggagg ggctcctgag gccacggrac agtgacttcc
caagtatcyt gcgcsgcgtc ttctaccgtc cctacctgca gatcttcggg cagattcccc
                                                                        60
aggaggacat ggacgtggcc ctcatggagc acagcaactg ytcgtcggag cccggcttct
                                                                       120
gggcacaccc tcctggggcc caggcgggca cctgcgtctc ccagtatgcc aactggctgg
                                                                       180
tggtgctgct cctcgtcatc ttcctgctcg tggccaacat cctgctggtc aacttgctca
                                                                       240
ttgccatgtt cagttacaca ttcggcaaag tacagggcaa cagcgatctc tactgggaag
                                                                       300
gcgcagcgtt accgcctcat ccgg
                                                                       360
                                                                       384
      <210> 186
      <211> 577
```

```
<212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(577)
      \langle 223 \rangle n = A.T.C or G
      <400> 186
gagttagete etceacaace ttgatgaggt egtetgeagt ggeetetege tteatacege
                                                                         60
tnccatcgtc atactgtagg tttgccacca cytcctggca tcttggggcg gcntaatatt
                                                                        120
ccaggaaact ctcaatcaag tcaccgtcga tgaaacctgt gggctggttc tgtcttccqc
                                                                        180
teggtgtgaa aggateteee agaaggagtg etegatette eccacaettt tgatgaettt
                                                                        240
attgagtcga ttctgcatgt ccagcaggag gttgtaccag ctctctgaca gtgaggtcac
                                                                        300
cagecetate atgeegttga megtgeegaa gareacegag eettgtgtgg gggkkgaagt
                                                                        360
ctcacccaga ttctgcatta ccagagagcc gtggcaaaag acattgacaa actcgcccag
                                                                        420
gtggaaaaag amcameteet ggargtgetn geegeteete gtemgttggt ggeagegetw
                                                                        480
tccttttgac acacaaacaa gttaaaggca ttttcagccc ccagaaantt gtcatcatcc
                                                                        540
aagatntcgc acagcactna tccagttggg attaaat
                                                                        577
      <210> 187
      <211> 534
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(534)
      \langle 223 \rangle n = A,T,C or G
      <400> 187
aacatcttcc tgtataatgc tgtgtaatat cgatccgatn ttgtctgstg agaatycatw
                                                                         60
actkggaaaa gmaacattaa agcctggaca ctggtattaa aattcacaat atgcaacact
                                                                        120
ttaaacagtg tgtcaatctg ctcccyynac tttgtcatca ccagtctggg aakaagggta
                                                                        180
tgccctattc acacctgtta aaagggcgct aagcattttt gattcaacat ctttttttt
                                                                        240
gacacaagtc cgaaaaaagc aaaagtaaac agttatyaat ttgttagcca attcactttc
                                                                        300
ttcatgggac agagccatyt gatttaaaaa gcaaattgca taatattgag cttygggagc
                                                                        360
tgatatttga gcggaagagt agcctttcta cttcaccaga cacaactccc tttcatattg
                                                                        420
ggatgttnac naaagtwatg tctctwacag atgggatgct tttgtggcaa ttctgttctg
                                                                        480
aggatetece agtttattta ceaettgeae aagaaggegt tttetteete agge
                                                                        534
      <210> 188
      <211> 761
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(761)
      \langle 223 \rangle n = A,T,C or G
      <400> 188
agaaaccagt atctctnaaa acaacctctc ataccttgtg gacctaattt tgtgtgcgtg
                                                                         60
tgtgtgtgcg cgcatattat atagacaggc acatcttttt tacttttgta aaagcttatg
                                                                        120
cctctttggt atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct
                                                                        180
```

```
ttgtcttctg tgtaaatggt actagagaaa acacctatnt tatgagtcaa tctagttngt
 tttattcgac atgaaggaaa tttccagatn acaacactna caaactctcc ctkgackarg
                                                                         240
 ggggacaaag aaaagcaaaa ctgamcataa raaacaatwa cctggtgaga arttgcataa
                                                                         300
 acagaaatwr ggtagtatat tgaarnacag catcattaaa rmgttwtktt wttctccctt
                                                                         360
 gcaaaaaaca tgtacngact tcccgttgag taatgccaag ttgttttttt tatnataaaa
                                                                         420
 cttgcccttc attacatgtt tnaaagtggt gtggtgggcc aaaatattga aatgatggaa
                                                                         480
 ctgactgata aagctgtaca aataagcagt gtgcctaaca agcaacacag taatgttgac
                                                                         540
 atgettaatt cacaaatget aattteatta taaatgtttg etaaaataca etttgaacta
                                                                         600
 tttttctgtn ttcccagagc tgagatntta gattttatgt agtatnaagt gaaaaantac
                                                                        660
 gaaaataata acattgaaga aaaananaaa aaanaaaaaa a
                                                                        720
                                                                        761
       <210> 189
       <211> 482
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(482)
       \langle 223 \rangle n = A,T,C or G
       <400> 189
tttttttttt tttgccgatn ctactatttt attgcaggan gtgggggtgt atgcaccgca
caccggggct atnagaagca agaaggaagg agggaggca cagccccttg ctgagcaaca
                                                                         60
aagccgcctg ctgccttctc tgtctgtctc ctggtgcagg cacatgggga gaccttcccc
                                                                        120
aaggcagggg ccaccagtcc aggggtggga atacaggggg tgggangtgt gcataagaag
                                                                        180
tgataggcac aggccacccg gtacagaccc ctcggctcct gacaggtnga tttcgaccag
                                                                        240
gtcattgtgc cctgcccagg cacagcgtan atctggaaaa gacagaatgc tttccttttc
                                                                        300
aaatttggct ngtcatngaa ngggcanttt tccaanttng gctnggtctt ggtacnettg
                                                                        360
gttcggccca gctccncgtc caaaaantat tcacccnnct ccnaattgct tgcnggnccc
                                                                        420
                                                                        480
CC
                                                                        482
      <210> 190
      <211> 471
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(471)
      <223> n = A,T,C or G
      <400> 190
ttttttttt ttttaaaaca gttttcaca acaaaattta ttagaagaat agtggttttg
aaaactctcg catccagtga gaactaccat acaccacatt acagctngga atgtnctcca
                                                                        60
aatgtctggt caaatgatac aatggaacca ttcaatctta cacatgcacg aaagaacaag
                                                                       120
cgcttttgac atacaatgca caaaaaaaaa aggggggggg gaccacatgg attaaaattt
                                                                       180
taagtactca tcacatacat taagacacag ttctagtcca gtcnaaaatc agaactgcnt
                                                                       240
tgaaaaattt catgtatgca atccaaccaa agaacttnat tggtgatcat gantneteta
                                                                       300
ctacatcnac cttgatcatt gccaggaacn aaaagttnaa ancacncngt acaaaaanaa
                                                                       360
totgtaattn anttoaacet cogtaongaa aaatnttnnt tatacactoo c
                                                                       420
                                                                       471
      <210> 191
      <211> 402
     <212> DNA
```

```
<213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (402)
      \langle 223 \rangle n = A,T,C or G
      <400> 191
gagggattga aggtctgttc tastgtcggm ctgttcagcc accaactcta acaagttgct
                                                                          60
gtcttccact cactgtctgt aagcttttta acccagacwg tatcttcata aatagaacaa
                                                                         120
attetteace agteacatet tetaggacet ttttggatte agttagtata agetetteea
                                                                         180
cttcctttgt taagacttca tctggtaaag tcttaagttt tgtagaaagg aattyaattg
                                                                         240
ctcgttctct aacaatgtcc tctccttgaa gtatttggct gaacaaccca cctaaagtcc
                                                                         300
ctttqtqcat ccattttaaa tatacttaat agggcattgk tncactaggt taaattctgc
                                                                         360
aagagtcatc tgtctgcaaa agttgcgtta gtatatctgc ca
                                                                         402
      <210> 192
      <211> 601
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (601)
      \langle 223 \rangle n = A,T,C or G
      <400> 192
gageteggat ceaataatet ttgtetgagg geageacaea tatneagtge catggnaact
                                                                         60
ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac
                                                                         120
atgcytyttt gaytaccgtg tgccaagtgc tggtgattct yaacacacyt ccatcccgyt
                                                                         180
cttttgtgga aaaactggca cttktctgga actagcarga catcacttac aaattcaccc
                                                                         240
acgagacact tgaaaggtgt aacaaagcga ytcttgcatt gctttttgtc cctccggcac
                                                                         300
cagttgtcaa tactaacccg ctggtttgcc tccatcacat ttgtgatctg tagctctgga
                                                                        360
tacatetect gacagtactg aagaacttet tettttgttt caaaageare tettggtgee
                                                                        420
tgttggatca ggttcccatt tcccagtcyg aatgttcaca tggcatattt wacttcccac
                                                                        480
aaaacattgc gatttgaggc tcagcaacag caaatcctgt tccggcattg gctgcaaqag
                                                                        540
cctcgatgta gccggccagc gccaaggcag gcgccgtgag ccccaccagc agcagaagca
                                                                        600
                                                                        601
      <210> 193
      <211> 608
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(608)
      \langle 223 \rangle n = A,T,C or G
      <400> 193
atacagecea nateceacea egaagatgeg ettgttgaet gagaacetga tgeggteaet
                                                                         60
ggtcccgctg tagccccagc gactctccac ctgctggaag cggttgatgc tgcactcytt
                                                                        120
cccaacgcag gcagmagcgg gsccggtcaa tgaactccay tcgtggcttg gggtkgacgg
                                                                        180
tkaagtgcag gaagaggctg accacctcgc ggtccaccag gatgcccgac tgtgcgggac
                                                                        240
ctgcagcgaa actcctcgat ggtcatgagc gggaagcgaa tgaggcccag ggccttgccc
                                                                        300
```

```
agaaccttcc gcctgttctc tggcgtcacc tgcagctgct gccgctgaca ctcggcctcg
 gaccagegga caaacggert tgaacageeg caceteaegg atgeceagtg tgtegegete
                                                                          360
 caggammgsc accagegtgt ccaggtcaat gteggtgaag cceteegegg gtratggegt
                                                                          420
 ctgcagtgtt tttgtcgatg ttctccaggc acaggctggc cagctgcggt tcatcgaaga
                                                                          480
 gtcgcgcctg cgtgagcagc atgaaggcgt tgtcggctcg cagttcttct tcaggaactc
                                                                          540
                                                                          600
 cacgcaat
                                                                          608
       <210> 194
       <211> 392
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(392)
       \langle 223 \rangle n = A,T,C or G
       <400> 194
 gaacggctgg accttgcctc gcattgtgct tgctggcagg gaataccttg gcaagcagyt
 ccagtccgag cagccccaga ccgctgccgc ccgaagctaa gcctgcctct ggccttcccc
                                                                          60
 tecgeeteaa tgeagaacea gtagtgggag caetgtgttt agagttaaga gtgaacaetg
                                                                         120
tttgatttta cttgggaatt tcctctgtta tatagctttt cccaatgcta atttccaaac
                                                                         180
aacaacaaca aaataacatg tttgcctgtt aagttgtata aaagtagqtg attctgtatt
                                                                         240
taaagaaaat attactgtta catatactgc ttgcaatttc tgtatttatt gktnctstgg
                                                                         300
                                                                         360
aaataaatat agttattaaa ggttgtcant cc
                                                                         392
       <210> 195
       <211> 502
       <212> DNA
       <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(502)
      \langle 223 \rangle n = A,T,C or G
      <400> 195
ccsttkgagg ggtkaggkyc cagttyccga gtggaagaaa caggccagga gaagtgcgtg
ccgagctgag gcagatgttc ccacagtgac ccccagagcc stgggstata gtytctgacc
                                                                         60
cctcncaagg aaagaccacs ttctggggac atgggctgga gggcaggacc tagaggcacc
                                                                        120
aagggaaggc cccattccgg ggstgttccc cgaggaggaa gggaagggc tctgtgtgcc
                                                                        180
ccccasgagg aagaggccct gagtcctggg atcagacacc ccttcacgtg tatccccaca
                                                                        240
caaatgcaag ctcaccaagg tcccctctca gtccccttcc stacaccctg amcggccact
                                                                        300
gscscacacc cacccagage acgccacccg ccatggggar tgtgctcaag gartcgcngg
                                                                        360
gcarcgtgga catctngtcc cagaaggggg cagaatctcc aatagangga ctgarcmstt
                                                                        420
                                                                        480
gctnanaaaa aaaaanaaaa aa
                                                                        502
      <210> 196
      <211> 665
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(665)
```

```
<223> n = A, T, C \text{ or } G
      <400> 196
ggttacttgg tttcattgcc accacttagt ggatgtcatt tagaaccatt ttgtctgctc
                                                                         60
cetetggaag cettgegeag ageggaettt gtaattgttg gagaataact getgaatttt
                                                                        120
wagctgtttk gagttgatts gcaccactgc acccacaact tcaatatgaa aacyawttga
                                                                        180
actwatttat tatcttgtga aaagtataac aatgaaaatt ttgttcatac tgtattkatc
                                                                        240
aagtatgatg aaaagcaawa gatatatatt cttttattat gttaaattat gattgccatt
                                                                        300
attaatcggc aaaatgtgga gtgtatgttc ttttcacagt aatatatgcc ttttgtaact
                                                                        360
tcacttggtt attttattgt aaatgartta caaaattctt aatttaagar aatggtatgt
                                                                        420
watatttatt tcattaattt ctttcctkgt ttacgtwaat tttgaaaaga wtgcatgatt
                                                                        480
tettgacaga aategatett gatgetgtgg aagtagtttg acceacatee etatgagttt
                                                                        540
ttcttagaat gtataaaggt tgtagcccat cnaacttcaa agaaaaaaat gaccacatac
                                                                        600
tttgcaatca ggctgaaatg tggcatgctn ttctaattcc aactttataa actagcaaan
                                                                        660
aagtg
                                                                        665
      <210> 197
      <211> 492
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(492)
      \langle 223 \rangle n = A,T,C or G
      <400> 197
ttttnttttt tttttttgc aggaaggatt ccatttattg tggatgcatt ttcacaatat
                                                                        60
atgtttattg gagcgatcca ttatcagtga aaagtatcaa gtgtttataa natttttagg
                                                                        120
aaggcagatt cacagaacat gctngtcngc ttgcagtttt acctcgtana gatnacagag
                                                                        180
aattatagtc naaccagtaa acnaggaatt tacttttcaa aagattaaat ccaaactgaa
                                                                        240
caaaattcta ccctgaaact tactccatcc aaatattgga ataanagtca gcagtgatac
                                                                        300
attetettet gaactttaga tittetagaa aaatatgtaa tagtgateag gaagagetet
                                                                        360
tgttcaaaag tacaacnaag caatgttccc ttaccatagg ccttaattca aactttgatc
                                                                        420
catttcactc ccatcacggg agtcaatgct acctgggaca cttgtatttt gttcatnctg
                                                                        480
ancntggctt aa
                                                                        492
      <210> 198
      <211> 478
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(478)
      <223> n = A, T, C \text{ or } G
      <400> 198
tttnttttgn atttcantct gtannaanta ttttcattat gtttattana aaaatatnaa
                                                                        60
tgtntccacn acaaatcatn ttacntnagt aagaggccan ctacattgta caacatacac
                                                                        120
tgagtatatt ttgaaaagga caagtttaaa gtanacncat attgccganc atancacatt
                                                                        180
tatacatggc ttgattgata tttagcacag canaaactga gtgagttacc agaaanaaat
                                                                        240
natatatgtc aatcngattt aagatacaaa acagatccta tggtacatan catcntgtag
                                                                       300
gagttgtggc tttatgttta ctgaaagtca atgcagttcc tgtacaaaga gatggccgta
                                                                       360
agcattctag tacctctact ccatggttaa gaatcgtaca cttatgttta catatgtnca
                                                                       420
```

```
gggtaagaat tgtgttaagt naanttatgg agaggtccan gagaaaaatt tgatncaa
                                                                          478
        <210> 199
        <211> 482
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc_feature
        <222> (1)...(482)
        <223> n = A,T,C \text{ or } G
       <400> 199
 agtgacttgt cctccaacaa aaccccttga tcaagtttgt ggcactgaca atcagaccta
 tgctagttcc tgtcatctat tcgctactaa atgcagactg gaggggacca aaaaggggca
                                                                          60
 tcaactccag ctggattatt ttggagcctg caaatctatt cctacttgta cggactttga
                                                                         120
 agtgattcag tttcctctac ggatgagaga ctggctcaag aatatcctca tgcagcttta
                                                                         180
 tgaagccnac tctgaacacg ctggttatct nagatgagaa ncagagaaat aaagtcnaga
                                                                         240
 aaatttacct ggangaaaag aggettingg etggggacca teccattgaa eettetetta
                                                                         300
 anggacttta agaanaaact accacatgtn tgtngtatcc tggtgccngg ccgtttantg
                                                                         360
 aacningach neaccetthi ggaatanani ettgaengen teetgaacti geteetetge
                                                                         420
                                                                         480
 ga
                                                                         482
       <210> 200
       <211> 270
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1) ...(270)
       <223> n = A, T, C or G
       <400> 200
cggccgcaag tgcaactcca gctggggccg tgcggacgaa gattctgcca gcagttggtc
cgactgcgac gacggcggcg gcgacagtcg caggtgcagc gcgggcgcct ggggtcttgc
                                                                         60
aaggetgage tgacgeegca gaggtegtgt cacgteecac gacettgacg eegtegggga
                                                                        120
cageeggaac agageeggt gaangeggga ggeetegggg ageeeetegg gaagggegge
                                                                        180
                                                                        240
ccgagagata cgcaggtgca ggtggccgcc
                                                                        270
      <210> 201
      <211> 419
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(419)
      \langle 223 \rangle n = A,T,C or G
      <400> 201
tttttttttt ttttggaatc tactgcgagc acagcaggtc agcaacaagt ttattttgca
gctagcaagg taacagggta gggcatggtt acatgttcag gtcaacttcc tttgtcgtgg
                                                                         60
ttgattggtt tgtctttatg ggggcggggt ggggtagggg aaancgaagc anaantaaca
                                                                        120
tggagtgggt gcaccctccc tgtagaacct ggttacnaaa gcttggggca gttcacctgg
                                                                        180
                                                                       240
```

```
totgtgaccg toattttott gacatcaatg ttattagaag toaggatato ttttagagag
                                                                    300
tccactgtnt ctggagggag attagggttt cttgccaana tccaancaaa atccacntga
                                                                    360
aaaagttgga tgatncangt acngaatacc ganggcatan ttctcatant cggtggcca
                                                                    419
      <210> 202
      <211> 509
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(509)
      <223> n = A, T, C \text{ or } G
      <400> 202
60
tggcacttaa tccattttta tttcaaaatg tctacaaant ttnaatncnc cattatacng
                                                                   120
gtnattttnc aaaatctaaa nnttattcaa atntnagcca aantccttac ncaaatnnaa
                                                                   180
tacncncaaa aatcaaaaat atacntntct ttcagcaaac ttngttacat aaattaaaaa
                                                                   240
aatatatacg gctggtgttt tcaaagtaca attatcttaa cactgcaaac atntttnnaa
                                                                   300
qqaactaaaa taaaaaaaaa cactnccgca aaggttaaag ggaacaacaa attcntttta
                                                                   360
caacancnnc nattataaaa atcatatctc aaatcttagg ggaatatata cttcacacng
                                                                   420
ggatcttaac ttttactnca ctttgtttat ttttttanaa ccattgtntt gggcccaaca
                                                                   480
caatggnaat nccnccncnc tggactagt
                                                                   509
     <210> 203
     <211> 583
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(583)
     <223> n = A,T,C \text{ or } G
     <400> 203
tttttttttt tttttttga cccccctctt ataaaaaaca agttaccatt ttattttact
                                                                    60
tacacatatt tattttataa ttggtattag atattcaaaa qqcaqctttt aaaatcaaac
                                                                   120
taaatggaaa ctgccttaga tacataattc ttaggaatta gcttaaaatc tgcctaaagt
                                                                   180
gaaaatcttc tctagctctt ttgactgtaa atttttgact cttgtaaaac atccaaattc
                                                                   240
attitititit tooctatic aagtoaatti
                                                                   300
gcttctctag cctcatttcc tagctcttat ctactattag taagtggctt ttttcctaaa
                                                                   360
agggaaaaca ggaagagana atggcacaca aaacaaacat tttatattca tatttctacc
                                                                   420
tacgttaata aaatagcatt ttgtgaagcc agctcaaaag aaggcttaga tccttttatg
                                                                   480
tccattttag tcactaaacg atatcnaaag tgccagaatg caaaaggttt gtgaacattt
                                                                   540
attcaaaagc taatataaga tatttcacat actcatcttt ctg
                                                                   583
     <210> 204
     <211> 589
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(589)
```

```
<223> n = A, T, C \text{ or } G
        <400> 204
  tttttttttt tttttttt ttttttnctc ttctttttt ttganaatga ggatcgagtt
  tttcactctc tagatagggc atgaagaaaa ctcatctttc cagctttaaa ataacaatca
                                                                          60
  aatotottat gotatatoat attitaagti aaactaatga gioactggot tatottotoo
                                                                          120
  tgaaggaaat ctgttcattc ttctcattca tatagttata tcaagtacta ccttgcatat
                                                                         180
  tgagaggttt ttcttctcta tttacacata tatttccatg tgaatttgta tcaaaccttt
                                                                         240
 attttcatgc aaactagaaa ataatgtntt cttttgcata agagaagaga acaatatnag
                                                                         300
 cattacaaaa ctgctcaaat tgtttgttaa gnttatccat tataattagt tnggcaggag
                                                                         360
 ctaatacaaa tcacatttac ngacnagcaa taataaaact gaagtaccag ttaaatatcc
                                                                         420
 aaaataatta aaggaacatt tttagcctgg gtataattag ctaattcact ttacaagcat
                                                                         480
 ttattnagaa tgaattcaca tgttattatt ccntagccca acacaatgg
                                                                         540
                                                                         589
       <210> 205
       <211> 545
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(545)
       \langle 223 \rangle n = A,T,C or G
       <400> 205
 tttttntttt ttttttcagt aataatcaga acaatattta tttttatatt taaaattcat
 agaaaagtgc cttacattta ataaaagttt gtttctcaaa gtgatcagag gaattagata
                                                                         60
 tngtcttgaa caccaatatt aatttgagga aaatacacca aaatacatta agtaaattat
                                                                         120
ttaagatcat agagcttyta agtgaaaaga taaaatttga cctcagaaac tctgagcatt
                                                                         180
aaaaatccac tattagcaaa taaattacta tggacttctt gctttaattt tgtgatgaat
                                                                        240
atggggtgtc actggtaaac caacacattc tgaaggatac attacttagt gatagattct
                                                                        300
tatgtacttt gctanatnac gtggatatga gttgacaagt ttctctttct tcaatctttt
                                                                        360
aaggggcnga ngaaatgagg aagaaaagaa aaggattacg catactgttc tttctatngg
                                                                        420
aaggattaga tatgtttcct ttgccaatat taaaaaaata ataatgttta ctactagtga
                                                                        480
                                                                        540
aaccc
                                                                        545
       <210> 206
       <211> 487
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (487)
      <223> n = A,T,C or G
      <400> 206
tttttttttt ttttttagtc aagtttctna tttttattat aattaaagtc ttggtcattt
catttattag ctctgcaact tacatattta aattaaagaa acgttnttag acaactgtna
                                                                         60
caatttataa atgtaaggtg ccattattga gtanatatat tcctccaaga gtggatgtgt
                                                                       120
cccttctccc accaactaat gaancagcaa cattagttta attttattag tagatnatac
                                                                       180
actgctgcaa acgctaattc tcttctccat ccccatgtng atattgtgta tatgtgtgag
                                                                       240
ttggtnagaa tgcatcanca atctnacaat caacagcaag atgaagctag gcntgggctt
                                                                       300
toggtgaaaa tagactgtgt ctgtctgaat caaatgatct gacctatcct cggtggcaag
                                                                       360
```

aactettega accgetteet caaaggenge tgecacattt gtggentetn ttgeacttgt

```
ttcaaaa
                                                                         487
      <210> 207
      <211> 332
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (332)
      \langle 223 \rangle n = A,T,C or G
      <400> 207
tgaattggct aaaagactgc atttttanaa ctagcaactc ttatttcttt cctttaaaaa
                                                                         60
tacatagcat taaatcccaa atcctattta aagacctgac agcttgagaa ggtcactact
                                                                         120
gcatttatag gaccttctgg tggttctgct gttacntttg aantctgaca atccttgana
                                                                         180
atctttgcat gcagaggagg taaaaggtat tggattttca cagaggaana acacagcgca
                                                                        240
gaaatgaagg ggccaggctt actgagcttg tccactggag ggctcatggg tgggacatgg
                                                                        300
aaaagaaggc agcctaggcc ctggggagcc ca
                                                                        332
      <210> 208
      <211> 524
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(524)
      \langle 223 \rangle n = A,T,C or G
      <400> 208
agggcgtggt gcggagggcg ttactgtttt gtctcagtaa caataaatac aaaaagactg
                                                                         60
gttgtgttcc ggccccatcc aaccacgaag ttgatttctc ttgtgtgcag agtgactgat
                                                                        120
tttaaaggac atggagcttg tcacaatgtc acaatgtcac agtgtgaagg gcacactcac
                                                                        180
tcccgcgtga ttcacattta gcaaccaaca atagctcatg agtccatact tgtaaatact
                                                                        240
tttggcagaa tacttnttga aacttgcaga tgataactaa gatccaagat atttcccaaa
                                                                        300
gtaaatagaa gtgggtcata atattaatta cctgttcaca tcagcttcca tttacaagtc
                                                                        360
atgageceag acactgaeat caaactaage ceaettagae teeteaceae cagtetgtee
                                                                        420
tgtcatcaga caggaggctg tcaccttgac caaattctca ccagtcaatc atctatccaa
                                                                        480
aaaccattac ctgatccact tccggtaatg caccaccttg gtga
                                                                        524
      <210> 209
      <211> 159
      <212> DNA
      <213> Homo sapien
      <400> 209
gggtgaggaa atccagagtt gccatggaga aaattccagt gtcagcattc ttgctccttg
                                                                         60
tggccctctc ctacactctg gccagagata ccacagtcaa acctggagcc aaaaaggaca
                                                                        120
caaaggactc tcgacccaaa ctgccccaga ccctctcca
                                                                        159
      <210> 210
      <211> 256
      <212> DNA
      <213> Homo sapien
```

```
<220>
        <221> misc_feature
        <222> (1)...(256)
        <223> n = A,T,C or G
        <400> 210
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 actgaatttc tttccacttg gactattaca tgccanttga gggactaatg gaaaaacgta
                                                                           60
 tggggagatt ttanccaatt tangtntgta aatggggaga ctggggcagg cgggagagat
                                                                          120
 ttgcagggtg naaatgggan ggctggtttg ttanatgaac agggacatag gaggtaggca
                                                                          180
                                                                          240
 ccaggatgct aaatca
                                                                         256
       <210> 211
       <211> 264
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(264)
       <223> n = A,T,C \text{ or } G
       <400> 211
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actggaacac atacccacat ctttgttctg agggataatt ttctgataaa gtcttgctgt
                                                                          60
atattcaagc acatatgtta tatattattc agttccatgt ttatagccta gttaaggaga
                                                                         120
ggggagatac attcngaaag aggactgaaa gaaatactca agtnggaaaa cagaaaaaga
                                                                         180
aaaaaaggag caaatgagaa gcct
                                                                         240
                                                                         264
       <210> 212
       <211> 328
       <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(328)
      \langle 223 \rangle n = A,T,C or G
      <400> 212
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ggatttaatg ttgtctcagc ttgggcactt cagttaggac ctaaggatgc cagccggcag
                                                                         60
gtttatatat gcagcaacaa tattcaagcg cgacaacagg ttattgaact tgcccgccag
                                                                        120
ttnaatttca ttcccattga cttgggatcc ttatcatcag ccagagagat tgaaaattta
                                                                        180
cccctacnac tctttactct ctgganaggg ccagtggtgg tagctataag cttggccaca
                                                                        240
                                                                        300
ttttttttc ctttattcct ttgtcaga
                                                                        328
      <210> 213
      <211> 250
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
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<222> (1)...(250)
      <223> n = A, T, C \text{ or } G
      <400> 213
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taaagcattg ctcactgaag ggatagaagt gactgccagg agggaaagta agccaaggct
                                                                         120
cattatgcca aagganatat acatttcaat tctccaaact tcttcctcat tccaagagtt
                                                                         180
ttcaatattt gcatgaacct gctgataanc catgttaana aacaaatatc tctctnacct
                                                                         240
tctcatcqqt
                                                                         250
      <210> 214
      <211> 444
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(444)
      \langle 223 \rangle n = A,T,C or G
      <400> 214
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                                                                          60
gatttaatgt tgtctcagct tgggcacttc agttaggacc taaggatgcc agccggcagg
                                                                         120
tttatatatg cagcaacaat attcaagcgc gacaacaggt tattgaactt gcccgccagt
                                                                         180
tgaatttcat tcccattgac ttgggatcct tatcatcagc canagagatt gaaaatttac
                                                                         240
ccctacgact ctttactctc tggagagggc cagtggtggt agctataagc ttggccacat
                                                                         300
ttttttttcc tttattcctt tgtcagagat gcgattcatc catatgctan aaaccaacag
                                                                         360
agrgactitt acaaaattcc tataganatt gigaataaaa ccitacciat agitgccatt
                                                                         420
actitgctct ccctaatata cctc
                                                                         444
      <210> 215
      <211> 366
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (366)
      \langle 223 \rangle n = A,T,C or G
      <400> 215
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                                                                         60
taaagcattg ctcactgaag ggatagaagt gactgccagg agggaaagta agccaaggct
                                                                        120
cattatgcca aagganatat acatttcaat tctccaaact tcttcctcat tccaagagtt
                                                                        180
ttcaatattt gcatgaacct gctgataagc catgttgaga aacaaatatc tctctgacct
                                                                        240
tctcatcggt aagcagaggc tgtaggcaac atggaccata gcgaanaaaa aacttagtaa
                                                                        300
tccaagctgt tttctacact gtaaccaggt ttccaaccaa ggtggaaatc tcctatactt
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ggtgcc
                                                                        366
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      <211> 260
      <212> DNA
      <213> Homo sapien
      <220>
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<221> misc feature
        <222> (1)...(260)
        <223> n = A,T,C \text{ or } G
        <400> 216
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                                                                           60
 caagacaggg gcctaaggag ggtctccaca ctgctnntaa gggctnttnc attttttat
 taataaaaag tnnaaaaggc ctcttctcaa cttttttccc ttnggctgga aaatttaaaa
                                                                          120
 atcaaaaatt tootnaagtt ntcaagctat catatatact ntatootgaa aaagcaacat
                                                                          180
                                                                          240
 aattcttcct tccctccttt
                                                                          260
       <210> 217
       <211> 262
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1) ... (262)
       <223> n = A, T, C \text{ or } G
       <400> 217
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 tottgootat aattitotat titaataagg aaatagcaaa tiggggtggg gggaatgtag
                                                                          60
 ggcattctac agtttgagca aaatgcaatt aaatgtggaa ggacagcact gaaaaatttt
                                                                         120
atgaataatc tgtatgatta tatgtctcta gagtagattt ataattagcc acttacccta
                                                                         180
                                                                         240
 atateettea tgettgtaaa gt
                                                                         262
       <210> 218
       <211> 205
       <212> DNA
       <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (205)
      \langle 223 \rangle n = A,T,C or G
      <400> 218
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cccctatcaa ctcccttttg tagtaaactt ggaaccttgg aaatgaccag gccaagactc
aggeeteece agttetactg acetttgtee ttangtntna ngtecagggt tgetaggaaa
                                                                         120
                                                                         180
anaaatcagc agacacaggt gtaaa
                                                                         205
      <210> 219
      <211> 114
      <212> DNA
      <213> Homo sapien
      <400> 219
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                                                                         60
                                                                        114
      <210> 220
      <211> 93
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<212> DNA
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      <400> 220
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aaataagcat ttagtgctca gtccctactq aqt
                                                                         93
      <210> 221
      <211> 167
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
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      \langle 223 \rangle n = A,T,C or G
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tettttgece ageetgtgge tetactgtag taagtttetg etgatgagga geeagnatge
                                                                       120
ccccactac cttccctgac gctccccana aatcacccaa cctctgt
                                                                       167
      <210> 222
      <211> 351
      <212> DNA
      <213> Homo sapien
      <400> 222
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gttcttcacc tgtcccccaa tccttaaaag gccatactgc ataaagtcaa caacagataa
                                                                       120
atgtttgctg aattaaagga tggatgaaaa aaattaataa tgaatttttg cataatccaa
                                                                       180
ttttctcttt tatatttcta gaagaagttt ctttgagcct attagatccc gggaatcttt
                                                                       240
taggtgagca tgattagaga gcttgtaggt tgcttttaca tatatctggc atatttgagt
                                                                       300
ctcgtatcaa aacaatagat tggtaaaggt ggtattattg tattgataag t
                                                                       351
      <210> 223
      <211> 383
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (383)
      <223> n = A, T, C or G
      <400> 223
aaaacaaaca aacaaaaaaa acaattcttc attcagaaaa attatcttag ggactgatat
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                                                                       120
ttaaaaatgtc tgtgccaaaa ttttgtattt tatttggaga cttcttatca aaagtaatgc
                                                                       180
tgccaaagga agtctaagga attagtagtg ttcccmtcac ttgtttggag tgtgctattc
                                                                       240
taaaaagattt tgatttcctg gaatgacaat tatattttaa ctttggtggg ggaaanagtt
                                                                       300
ataggaccac agticticact totgatacti gtaaattaat ottitatigo actigititg
                                                                       360
accattaagc tatatgttta aaa
                                                                       383
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<210> 224

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<211> 320
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        <213> Homo sapien
        <400> 224
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 aaaagtttgt gacattgtag tagggagtgt gtacccctta ctccccatca aaaaaaaaat
                                                                       60
 ggatacatgg ttaaaggata raagggcaat attttatcat atgttctaaa agagaaggaa
                                                                      120
 gagaaaatac tactttctcr aaatggaagc ccttaaaggt gctttgatac tgaaggacac
                                                                      180
 aaatgtggcc gtccatcctc ctttaragtt gcatgacttg gacacggtaa ctgttgcagt
                                                                      240
                                                                      300
 tttaractcm gcattgtgac
                                                                      320
       <210> 225
       <211> 1214
       <212> DNA
       <213> Homo sapien
       <400> 225
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                                                                      60
 aactcctaca ccatcgggct gggcctgcac agtcttgagg ccgaccaaga gccagggagc
                                                                      120
 cagatggtgg aggccagcct ctccgtacgg cacccagagt acaacagacc cttgctcgct
                                                                      180
 aacgacctca tgctcatcaa gttggacgaa tccgtgtccg agtctgacac catccggagc
                                                                     240
 atcagcattg cttcgcagtg ccctaccgcg gggaactett gcctcgtttc tggctggggt
                                                                     300
 ctgctggcga acggcagaat gcctaccgtg ctgcagtgcg tgaacgtgtc ggtggtgtct
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gaggaggtct gcagtaagct ctatgacccg ctgtaccacc ccagcatgtt ctgcgccggc
                                                                     420
ggagggcaag accagaagga ctcctgcaac ggtgactctg gggggcccct gatctgcaac
                                                                     480
gggtacttgc agggccttgt gtctttcgga aaagccccgt gtggccaagt tggcgtgcca
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ggtgtctaca ccaacctctg caaattcact gagtggatag agaaaaccgt ccaggccagt
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taactctggg gactgggaac ccatgaaatt gacccccaaa tacatcctgc ggaaggaatt
                                                                     660
caggaatate tgttcccage ceeteetee teaggeceag gagtccagge ecceagecee
                                                                     720
tectecetea aaccaagggt acagateeec ageceeteet eecteagace caggagteea
                                                                     780
gacccccag ccctcctcc ctcagaccca ggagtccagc ccctcctccc tcagacccag
                                                                     840
gagtccagac cccccagccc ctcctccctc agacccaggg gtccaggccc ccaacccctc
                                                                     900
ctccctcaga ctcagaggtc caagccccca acccctcctt ccccagaccc agaggtccag
                                                                     960
gtcccagccc ctcctccctc agacccagcg gtccaatgcc acctagactc tccctgtaca
                                                                    1020
cagtgccccc ttgtggcacg ttgacccaac cttaccagtt ggtttttcat tttttgtccc
                                                                    1080
1140
                                                                    1200
aaaaaaaaa aaaa
                                                                    1214
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      <400> 226
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agaacctggc ccagtcataa tcattcatcc tgacagtggc aataatcacg ataaccagt
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                                                                    119
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      <211> 818
      <212> DNA
     <213> Homo sapien
     <400> 227
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gagaaagcca	cgctcggcct	tctctgaacc	aggatggaac	ggcagacccc	tgaaaacgaa	300	
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agggcctcct	caggagcagt	ccaagagttt	tcaaagataa	cgtgacaact	accatctaga	420	
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caagaggata	tgaggactgt	ctcagcctgg	ctttgggctg	acaccatgca	cacacacaag	780	
greeaerrer	aggttttcag	cctagatggg	agtcgtgt			818	
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	> DNA						
	> Homo sapi	en					
	> 228						
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Coatactata	ctggccactc	cctcctaaaa	cacaggcgcc	ctcctggtga	cagtgacccg	540	
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ttaggagata	taatgttttt	atocastos	agetgtette	atttcctggg	ctaagcagca	660	
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	> DNA						
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	> 230						
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  cgggaaggga gagatgcctc cctctcattg aatgagcatc tccaggccct cctcactccg
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                                                                         240
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                                                                        60
cctagaagtt acagagcatc tagctggtgc gctggcaccc ctggcctcac acagactccc
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                                                                       180
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tacaaattaa catgagatga gtagagactt tattgagaaa gcaagagaaa atcctatcaa
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С
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tcaatttcag caacatactt ctcaatttct tcaggattta aaatcttgag ggattgatct
                                                                       120
cgcctcatga cagcaagttc aatgtttttg ccacctgact gaaccacttc caggagtgcc
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tgettteact aatgtetetg aacttetgte eetetttgtt eatggatagt eea atgttatett tgaactgatg eteataggag agaatataag aactetgagt gat	ataaata 180
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toggagoago atoattaata ooaagoagaa tgogtaatag ataaatacaa tgg	atatag 180
tgggtagacg gcttcatgag tacagtgtac tgtggtatcg taatctggac ttgg	ggttgta 240
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t	301
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ccttgagact tccggagtcg aggctctcca gggttcccca gcccatcaat catt	ttctgc 180
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212	501
<210> 239 · <211> 239	
\411\2033	

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   ttctgtcaaa ccatgatact gagctttgtg acaacccaga aataactaag agaaggcaaa
                                                                           60
   cataatacct tagagatcaa gaaacattta cacagttcaa ctgtttaaaa atagctcaac
                                                                          120
   attcagccag tgagtagagt gtgaatgcca gcatacacag tatacaggtc cttcaggga
                                                                          180
                                                                          239
         <210> 240
         <211> 300
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  gggatctgcc ctccagtgga accttttaag gaagaagtgg gcccaagcta agttccacat
                                                                          60
  gctgggtgag ccagatgact tctgttccct ggtcactttc ttcaatgggg cgaatggggg
                                                                         120
  ctgccaggtt tttaaaatca tgcttcatct tgaagcacac ggtcacttca ccctcctcac
                                                                         180
  gctgtgggtg tactttgatg aaaataccca ctttgttggc ctttctgaag ctataatgtc
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                                                                         300
        <210> 241
        <211> 301
        <212> DNA
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 cctctttgga ggaaactcca gcagctatgt tggtgtctct gagggaatgc aacaaggctg
                                                                         60
 ctcctccatg tattggaaaa ctgcaaactg gactcaactg gaaggaagtg ctgctgccag
                                                                        120
 tgtgaagaac cagcctgagg tgacagaaac ggaagcaaac aggaacagcc agtctttct
                                                                        180
 tectectect gteatacggt eteteteaag cateetttgt tgteagggge etaaaaggga
                                                                        240
                                                                        300
                                                                        301
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       <211> 301
       <212> DNA
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tgtggcattt cctcattttc tacattgtag aatcaagagt gtaaataaat gtatatcgat
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gtcttcaaga atatatcatt cctttttcac tagaacccat tcaaaatata agtcaagaat
                                                                       120
cttaatatca acaaatatat caagcaaact ggaaggcaga ataactacca taatttagta
                                                                       180
taagtaccca aagttttata aatcaaaagc cctaatgata accattttta gaattcaatc
                                                                       240
                                                                       300
                                                                       301
      <210> 243
      <211> 301
      <212> DNA
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ggtggcccaa gctatgaaat cagagggagg cttcatctgg gcctgtaaaa actatgatgg
                                                                       60
                                                                      120
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tgacgtgcag teggaetetg tggeecaagg gtatggetet eteggeatga tgaceagegt getggtttgt eeagatggea agacagtaga ageagagget geecaeggga etgtaaceeg teaetaeege atgtteeaga aaggaeagga gaegteeaee aateeeattg etteeatttt t	180 240 300 301
<210> 244 <211> 300 <212> DNA <213> Homo sapien	
<pre>&lt;400&gt; 244  gctggtttgc aagaatgaaa tgaatgattc tacagctagg acttaacctt gaaatggaaa gtcatgcaat cccatttgca ggatctgtct gtgcacatgc ctctgtagag agcagcattc ccagggacct tggaaacagt tgacactgta aggtgcttgc tccccaagac acatcctaaa aggtgttgta atggtgaaaa cgtcttcctt ctttattgcc ccttcttatt tatgtgaaca actgtttgtc ttttgtgtat ctttttaaa ctgtaaagtt caattgtgaa aatgaatatc</pre>	60 120 180 240 300
<210> 245 <211> 301 <212> DNA <213> Homo sapien	
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<210> 246 <211> 301 <212> DNA <213> Homo sapien	
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<210> 247 <211> 301 <212> DNA <213> Homo sapien	
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        <213> Homo sapien
        <400> 248
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 attaggaaga ttcttagggg taattttct gaggaaggag aactagccaa cttaagaatt
                                                                         60
 acaggaagaa agtggtttgg aagacagcca aagaaataaa agcagattaa attgtatcag
                                                                        120
 gtacattcca gcctgttggc aactccataa aaacatttca gattttaatc ccgaatttag
                                                                        180
 ctaatgagac tggatttttg ttttttatgt tgtgtgtcgc agagctaaaa actcagttcc
                                                                        240
                                                                        300
                                                                        301
       <210> 249
       <211> 301
       <212> DNA
       <213> Homo sapien
       <400> 249
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 ccctgacgct gctgttctcc ccgaaaaacc cgaccgacct ccgcgatctc cgtcccgccc
                                                                         60
 ccagggagac acagcagtga ctcagagctg gtcgcacact gtgcctccct cctcaccgcc
                                                                        120
 catcgtaatg aattattttg aaaattaatt ccaccatcct ttcagattct ggatggaaag
                                                                       180
                                                                       240
actgaatctt tgactcagaa ttgtttgctg aaaagaatga tgtgactttc ttagtcattt
                                                                       300
                                                                       301
       <210> 250
       <211> 301
       <212> DNA
       <213> Homo sapien
       <400> 250
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cttatcttta ttggcttgat aaacataatt atttctaaca ctagcttatt tccagttgcc
                                                                        60
cataagcaca toagtacttt tototggotg gaatagtaaa ctaaagtatg gtacatotac
                                                                       120
ctaaaagact actatgtgga ataatacata ctaatgaagt attacatgat ttaaagacta
                                                                       180
caataaaacc aaacatgctt ataacattaa gaaaaacaat aaagatacat gattgaaacc
                                                                       240
                                                                       300
                                                                       301
      <210> 251
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 251
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agacaacctc atagagcata ggagaactgg ttgccctggg ggcaggggga ctgtctggat
                                                                       60
ggcaggggtc ctcaaaaatg ccactgtcac tgccaggaaa tgcttctgag cagtacacct
                                                                      120
cattgggatc aatgaaaagc ttcaagaaat cttcaggctc actctcttga aggcccggaa
                                                                      180
cctctggagg ggggcagtgg aatcccagct ccaggacgga tcctgtcgaa aagatatcct
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                                                                      300
                                                                      301
      <210> 252
      <211> 301
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<212> DNA
       <213> Homo sapien
       <400> 252
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                                                                       120
 tcattccttt ttcactagga acccattcaa aatataagtc aagaatctta atatcaacaa
                                                                       180
 atatatcaag caaactggaa ggcagaataa ctaccataat ttagtataag tacccaaagt
 tttataaatc aaaagcccta atgataacca tttttagaat tcaatcatca ctgtagaatc
                                                                       240
                                                                       300
                                                                       301
       <210> 253
       <211> 301
       <212> DNA
       <213> Homo sapien
       <400> 253
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caactaaaaa aaaaaataa agaaaaaatg tgctgcgttc tgaaaaataa ctccttagct
                                                                        60
tggtctgatt gttttcagac cttaaaatat aaacttgttt cacaagcttt aatccatgtg
                                                                       120
                                                                       180
gattttttt cttagagaac cacaaaacat aaaaggagca agtcggactg aatacctgtt
tccatagtgc ccacagggta ttcctcacat tttctccata ggaaaatgct ttttcccaag
                                                                       240
                                                                       300
                                                                       301
      <210> 254
      <211> 301
      <212> DNA
      <213> Homo sapien
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aacttgacca attcccttga agcgggtggg ttaaaccctg taaatgggaa caaaatcccc
                                                                      120
ccaaatctct tcatcttacc ctggtggact cctgactgta gaattttttg gttgaaacaa
                                                                      180
gaaaaaaata aagctttgga cttttcaagg ttgcttaaca ggtactgaaa gactggcctc
acttaaactg agccaggaaa agctgcagat ttattaatgg gtgtgttagt gtgcagtgcc
                                                                      240
                                                                      300
t
                                                                      301
      <210> 255
      <211> 302
      <212> DNA
      <213> Homo sapien
      <400> 255
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attactgaaa tgtttctttt ctgaatataa atataaatat gtgcaaagtt tgacttggat
                                                                      120
tgggattttg ttgagttctt caagcatctc ctaataccct caagggcctg agtaggggg
aggaaaaagg actggaggtg gaatctttat aaaaaacaag agtgattgag gcagattgta
                                                                      180
                                                                      240
aacattatta aaaaacaaga aacaaacaaa aaaatagaga aaaaaaccac cccaacacac
                                                                      300
aa
                                                                      302
      <210> 256
     <211> 301
     <212> DNA
     <213> Homo sapien
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        <222> (1)...(301)
        <223> n = A, T, C \text{ or } G
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 aggaccetec tecceacace teatecace aaaccateca taatgeacee agataggeee
                                                                          60
 acceccaaaa geetggacae ettgageaca eagttatgae eaggacagae teatetetat
                                                                         120
 aggcaaatag ctgctggcaa actggcatta cctggtttgt ggggatgggg gggcaagtgt
                                                                         180
 gtggcctctc ggcctggtta gcaagaacat tcagggtagg cctaagttan tcgtgttagt
                                                                         240
                                                                         300
                                                                         301
       <210> 257
       <211> 301
       <212> DNA
       <213> Homo sapien
       <400> 257
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 tececaetta tttttgtett teactatege aggeettaga agaggtetae etgeeteeag
                                                                         60
 tettacetag tecagtetae eccetggagt tagaatggee atectgaagt gaaaagtaat
                                                                        120
 gtcacattac tcccttcagt gatttcttgt agaagtgcca atccctgaat gccaccaaga
                                                                        180
tottaatott cacatottta atottatoto tittgactoot otttacacog gagaaggoto
                                                                        240
                                                                        300
                                                                        301
       <210> 258
       <211> 301
       <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(301)
      <223> n = A,T,C or G
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aggggcccag ccaccaggcg cagaagcaag ataaacagta ggctcaagac cagagccacc
                                                                        60
cccagggcaa caagaatcca ataccaggac tgggcaaaat cttcaaagat cttaacactg
                                                                       120
atgtctcggg cattgaggct gtcaataana cgctgatccc ctgctgtatg gtggtgtcat
                                                                       180
tggtgatccc tgggagcgcc ggtggagtaa cgttggtcca tggaaagcag cgcccacaac
                                                                       240
                                                                       300
                                                                       301
      <210> 259
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
     <222> (1)...(301)
     <223> n = A,T,C or G
     <400> 259
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tcatatatgc aaacaaatgc agactangcc tcaggcagag actaaaggac atctcttggg
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 gtgtcctgaa gtgatttgga cccctgaggg cagacaccta agtaggaatc ccagtgggaa
                                                                       120
 gcaaagccat aaggaagccc aggattcctt gtgatcagga agtgggccag gaaggtctgt
                                                                       180
 tecageteae ateteatetg catgeageae ggaceggatg egeceaetgg gtettggett
                                                                       240
 ccctcccatc ttctcaagca gtgtccttgt tgagccattt gcatccttgg ctccaggtgg
                                                                       300
                                                                       301
       <210> 260
       <211> 301
       <212> DNA
       <213> Homo sapien
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aaggtgtctt aacttgaaaa agattaggag tcactggttt acaagttata attgaatgaa
                                                                       120
agaactgtaa cagccacagt tggccatttc atgccaatgg cagcaaacaa caggattaac
                                                                       180
tagggcaaaa taaataagtg tgtggaagcc ctgataagtg cttaataaac agactgattc
                                                                       240
actgagacat cagtacetge cegggeggee getegageeg aattetgeag atatecatea
                                                                       300
C
                                                                       301
      <210> 261
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 261
aaatattcga gcaaatcctg taactaatgt gtctccataa aaggctttga actcagtgaa
                                                                       60
tetgetteca tecaegatte tageaatgae eteteggaea teaaagetee tettaaggtt
                                                                      120
agcaccaact attccataca attcatcagc aggaaataaa ggctcttcag aaggttcaat
                                                                      180
ggtgacatcc aatttettet gataatttag attecteaca acetteetag ttaagtgaag
                                                                      240
ggcatgatga tcatccaaag cccagtggtc acttactcca gactttctgc aatgaagatc
                                                                      300
                                                                      301
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      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 262
gaggagagcc tgttacagca tttgtaagca cagaatactc caggagtatt tgtaattgtc
                                                                       60
tgtgagette ttgccgcaag tetetcagaa atttaaaaag atgcaaatee etgagteace
                                                                      120
cctagacttc ctaaaccaga tcctctgggg ctggaacctg gcactctgca tttgtaatga
                                                                      180
gggctttctg gtgcacacct aattttgtgc atctttgccc taaatcctgg attagtgccc
                                                                      240
catcattacc cccacattat aatgggatag attcagagca gatactctcc agcaaagaat
                                                                      300
                                                                      301
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      <211> 301
      <212> DNA
      <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(301)
     <223> n = A, T, C or G
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  aaaattacta cttaatccta attcacaata acaatggcat taaggtttga cttgagttgg
                                                                          60
  ttcttagtat tatttatggt aaataggctc ttaccacttg caaataactg gccacatcat
                                                                         120
  taatgactga cttcccagta aggctctcta aggggtaagt angaggatcc acaggatttg
                                                                         180
  agatgctaag gccccagaga tcgtttgatc caaccctctt attttcagag gggaaaatgg
                                                                         240
                                                                         300
                                                                         301
        <210> 264
        <211> 301
        <212> DNA
        <213> Homo sapien
        <400> 264
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 aatgaatgac tctaaaaaca atatttacat ttaatggttt gtagacaata aaaaaacaag
                                                                         60
 gtggatagat ctagaattgt aacattttaa gaaaaccata scatttgaca gatgagaaag
                                                                        120
 ctcaattata gatgcaaagt tataactaaa ctactatagt agtaaagaaa tacatttcac
                                                                        180
 accetteata taaatteact atettggett gaggeactee ataaaatgta teaegtgeat
                                                                        240
                                                                        300
                                                                        301
       <210> 265
       <211> 301
       <212> DNA
       <213> Homo sapien
       <400> 265
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 cttcttgtga cgcagtattt cttctctggg gagaagccgg gaagtcttct cctggctcta
                                                                        60
 catattettg gaagteteta atcaactttt gtteeatttg ttteatttet teaggaggga
                                                                       120
ttttcagttt gtcaacatgt tctctaacaa cacttgccca tttctgtaaa gaatccaaag
                                                                       180
cagtccaagg ctttgacatg tcaacaacca gcataactag agtatccttc agagatacgg
                                                                       240
                                                                       300
                                                                       301
      <210> 266
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 266
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acaccagate actetteet etacccacag gettgetatg ageaagagae acaaceteet
                                                                       60
ctcttctgtg ttccagcttc ttttcctgtt cttcccaccc cttaagttct attcctgggg
                                                                       120
atagagacac caatacccat aacctctctc ctaagcctcc ttataaccca gggtgcacag
                                                                      180
cacagactcc tgacaactgg taaggccaat gaactgggag ctcacagctg gctgtgcctg
                                                                      240
                                                                      300
                                                                      301
      <210> 267
     <211> 301
     <212> DNA
     <213> Homo sapien
     <400> 267
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aaagagcaca ggccagctca gcctgccctg gccatctaga ctcagcctgg ctccatgggg

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gttctcagtg ctgagtccat ccaggaaaag ctcacctaga ccttctgagg ctgaatcttc
                                                                       120
atcctcacag gcagcttctg agagcctgat attcctagcc ttgatggtct ggagtaaagc
                                                                       180
ctcattctga ttcctccct tctttcttt caagttggct ttcctcacat ccctctgttc
                                                                       240
aattcgcttc agcttgtctg ctttagccct catttccaga agcttcttct ctttggcatc
                                                                       300
                                                                       301
      <210> 268
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 268
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gatcttggga gagctggttc ttctaaggag aaggaggaag gacagatgta actttggatc
                                                                       120
tcgaagagga agtctaatgg aagtaattag tcaacggtcc ttgtttagac tcttggaata
                                                                       180
tgctgggtgg ctcagtgagc ccttttggag aaagcaagta ttattcttaa ggagtaacca
                                                                       240
cttcccattg ttctactttc taccatcatc aattgtatat tatgtattct ttggagaact
                                                                       300
                                                                       301
      <210> 269
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 269
taacaatata cactagctat ctttttaact gtccatcatt agcaccaatg aagattcaat
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aaaattacct ttattcacac atctcaaaac aattctgcaa attcttagtg aagtttaact
                                                                       120
atagtcacag accttaaata ttcacattgt tttctatgtc tactgaaaat aagttcacta
                                                                       180
cttttctgga tattctttac aaaatcttat taaaattcct ggtattatca ccccaatta
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tacagtagca caaccacctt atgtagtttt tacatgatag ctctgtagaa gtttcacatc
                                                                       300
                                                                       301
      <210> 270
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 270
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cacaagaata catatteett ttatttetaa ggagttaaac atagatgtag etgatgtgga
                                                                      120
gagettgetg gtgeagtgea tattggataa cactatteat ggeegaattg ateaagteaa
                                                                      180
ccaactcctt gaactggatc atcagaagaa gggtggtgca cgatatactg cactagataa
                                                                      240
tggaccaacc aactaaattc tctcaccagg ctgtatcagt aaactggctt aacagaaaac
                                                                      300
а
                                                                      301
     <210> 271
     <211> 301
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(301)
     <223> n = A,T,C or G
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  tttatagctc atctttaggg ttgatattca gttcatgctt cccttgctgt tcttgatcca
                                                                           60
  gaattgcaat cacttcatca gcctgtattc gctccaattc tctataaagt gggtccaagg
                                                                          120
  tgaaccacag agccacagca cacctettte cettggtgae tgeetteace ceatganggt
                                                                          180
  tetetectee agatganaac tgateatgeg eccacatttt gggttttata gaageagtea
                                                                          240
                                                                          300
                                                                          301
        <210> 272
        <211> 301
        <212> DNA
        <213> Homo sapien
        <400> 272
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  ttatcagaaa accaaatgag cctggaatct tcataatacc taaacatgcc gtatttagga
                                                                          60
  tccaataatt ccctcatgat gagcaagaaa aattctttgc gcacccctcc tgcatccaca
                                                                         120
 gcatcttctc caacaaatat aaccttgagt ggcttcttgt aatctatgtt ctttgttttc
                                                                         180
 ctaaggactt ccattgcatc tcctacaata ttttctctac gcaccactag aattaagcag
                                                                         240
                                                                         300
                                                                         301
        <210> 273
        <211> 301
        <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(301)
       <223> n = A,T,C or G
       <400> 273
 acatgtgtgt atgtgtatct ttgggaaaan aanaagacat cttgtttayt attttttgg
 agagangctg ggacatggat aatcacwtaa tttgctayta tyactttaat ctgactygaa
                                                                         60
 gaaccgtcta aaaataaaat ttaccatgtc dtatattcct tatagtatgc ttatttcacc
                                                                        120
 ttytttctgt ccagagagag tatcagtgac ananatttma gggtgaamac atgmattggt
                                                                        180
gggacttnty tttacngagm accetgeeg sgegeeeteg makengantt eegesanane
                                                                        240
                                                                       300
                                                                       301
       <210> 274
       <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(301)
      <223> n = A, T, C \text{ or } G
      <400> 274
cttatatact ctttctcaga ggcaaaagag gagatgggta atgtagacaa ttctttgagg
aacagtaaat gattattaga gagaangaat ggaccaagga gacagaaatt aacttgtaaa
                                                                        60
tgattctctt tggaatctga atgagatcaa gaggccagct ttagcttgtg gaaaagtcca
                                                                       120
tctaggtatg gttgcattct cgtcttcttt tctgcagtag ataatgaggt aaccgaaggc
                                                                       180
aattgtgctt cttttgataa gaagctttct tggtcatatc aggaaattcc aganaaagtc
                                                                       240
                                                                       300
```

```
С
                                                                         301
       <210> 275
       <211> 301
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(301)
       <223> n = A, T, C \text{ or } G
       <400> 275
tcggtgtcag cagcacgtgg cattgaacat tgcaatgtgg agcccaaacc acagaaaatg
                                                                         60
gggtgaaatt ggccaacttt ctattaactt atgttggcaa ttttgccacc aacagtaagc
                                                                        120
tggcccttct aataaaagaa aattgaaagg tttctcacta aacggaatta agtagtggag
                                                                        180
tcaagagact cccaggcetc agegtacctg cccgggeggc cgctcgaagc cgaattctgc
                                                                        240
agatatccat cacactggcg gncgctcgan catgcatcta gaaggnccaa ttcgccctat
                                                                        300
a
                                                                        301
      <210> 276
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 276
tgtacacata ctcaataaat aaatgactgc attgtggtat tattactata ctgattatat
                                                                         60
ttatcatgtg acttctaatt agaaaatgta tccaaaagca aaacagcaga tatacaaaat
                                                                        120
taaagagaca gaagatagac attaacagat aaggcaactt atacattgag aatccaaatc
                                                                        180
caatacattt aaacatttgg gaaatgaggg ggacaaatgg aagccagatc aaatttgtgt
                                                                        240
aaaactattc agtatgtttc ccttgcttca tgtctgagaa ggctctcctt caatggggat
                                                                        300
g
                                                                        301
      <210> 277
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(301)
      <223> n = A,T,C \text{ or } G
      <400> 277
tttgttgatg tcagtatttt attacttgcg ttatgagtgc tcacctggga aattctaaag
                                                                         60
atacagagga cttggaggaa gcagagcaac tgaatttaat ttaaaagaag gaaaacattg
                                                                        120
gaatcatggc actcctgata ctttcccaaa tcaacactct caatgcccca ccctcgtcct
                                                                        180
caccatagtg gggagactaa agtggccacg gatttgcctt angtgtgcag tgcgttctga
                                                                        240
gttenetgte gattacatet gaccagtete ettttteega agteenteeg tteaatettg
                                                                        300
                                                                       301
      <210> 278
      <211> 301
      <212> DNA
      <213> Homo sapien
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<220>
        <221> misc_feature
        <222> (1)...(301)
        <223> n = A, T, C \text{ or } G
        <400> 278
 taccactaca ctccagcctg ggcaacagag caagacctgt ctcaaagcat aaaatggaat
 aacatatcaa atgaaacagg gaaaatgaag ctgacaattt atggaagcca gggcttgtca
                                                                          60
 cagtetetae tgttattatg cattacetgg gaatttatat aageeettaa taataatgee
                                                                         120
 aatgaacatc tcatgtgtgc tcacaatgtt ctggcactat tataagtgct tcacaggttt
                                                                         180
 tatgtgttct tcgtaacttt atggantagg tactcggccg cgaacacgct aagccgaatt
                                                                         240
                                                                         300
                                                                         301
       <210> 279
       <211> 301
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1) ... (301)
       <223> n = A, T, C or G
       <400> 279
 aaagcaggaa tgacaaagct tgcttttctg gtatgttcta ggtgtattgt gacttttact
                                                                         60
gttatattaa ttgccaatat aagtaaatat agattatata tgtatagtgt ttcacaaagc
ttagacettt acettecage caceccacag tgettgatat tteagagtea gteattggtt
                                                                        120
atacatgtgt agttccaaag cacataagct agaanaanaa atatttctag ggagcactac
                                                                        180
catctgtttt cacatgaaat gccacacaca tagaactcca acatcaattt cattgcacag
                                                                        240
                                                                        300
                                                                        301
       <210> 280
       <211> 301
       <212> DNA
       <213> Homo sapien
      <400> 280
ggtactggag ttttcctccc ctgtgaaaac gtaactactg ttgggagtga attgaggatg
                                                                         60
tagaaaggtg gtggaaccaa attgtggtca atggaaatag gagaatatgg ttctcactct
tgagaaaaaa acctaagatt agcccaggta gttgcctgta acttcagttt ttctgcctgg
                                                                        120
gtttgatata gtttagggtt ggggttagat taagatctaa attacatcag gacaaagaga
                                                                        180
cagactatta actccacagt taattaagga ggtatgttcc atgtttattt gttaaagcag
                                                                        240
                                                                        300
t
                                                                        301
      <210> 281
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 281
aggtacaaga aggggaatgg gaaagagctg ctgctgtggc attgttcaac ttggatattc
gccgagcaat ccaaatcctg aatgaagggg catcttctga aaaaggagat ctgaatctca
                                                                        60
atgtggtagc aatggcttta tcgggttata cggatgagaa gaactccctt tggagagaaa
                                                                       120
tgtgtagcac actgcgatta cagctaaata acccgtattt gtgtgtcatg tttgcatttc
                                                                       180
                                                                       240
```

tgacaagtga aacaggatct tacgatggag ttttgtatga aaacaa g	agtt gcagtacctc 300
<210> 282 <211> 301 <212> DNA <213> Homo sapien	
<400> 282	
caggtactac agaattaaaa tactgacaag caagtagttt cttggc tccagaaccc aaaaattaag aaattcaaaa agacattttg tgggca agcgcagaag caaagcccag gcagaaccat gctaacctta cagctc cgcagaagca aagcccaggc agaaccatgc taaccttaca gctcag cagaagcaaa gcccaggcag aacatgctaa ccttacagct cagcct a	acctg ctagcacaga 120 agcc tgcacagaag 180 acctg cacagaagcg 240
<210> 283 <211> 301 <212> DNA <213> Homo sapien	
<400> 283	
atctgtatac ggcagacaaa ctttatarag tgtagagagg tgagcg cactttgagg gctttataat aatatgctgc ttgaaaaaaa aaatgt gtgcatctcc agacatagta aggggttgct ctgaccaatc aggtga acttcccagg ttttatgcaa aaattttgtt aaaattctata atggtg ggaaacatat acatttttaa aaatctattt tatgtaagaa ctgaca g	gtag ttgatactca 120 tcat tttttctatc 180 atat gcatctttta 240
<210> 284 <211> 301 <212> DNA <213> Homo sapien	
<400> 284	
caggtacaaa acgctattaa gtggcttaga atttgaacat ttgtggggcttcgtggg tgggcaaagc aacatcttcc ctaaatatat attacca gcagattagg tttttgacaa aacaaacagg ccaaaagggg gctgacaggtgagaggc aaggcatgag agggcaagtt tgttgtggac agatctgactggagtaa aagaaaacaa agttcattga tgtcgaagga tatataa a	aaga aaagcaagaa 120 ctgg agcagagcat 180 gtgc ctactttatt 240
<210> 285 <211> 301 <212> DNA <213> Homo sapien	
<220> <221> misc_feature <222> (1)(301) <223> n = A,T,C or G	
<400> 285 acatcaccat gatcggatcc cccacccatt atacgttgta tgtttacatgatcatt agtgtttaa aaaaaatact gaaaactcct tctgcat	cata aatactcttc 60 cccc aatctctaac 120

```
caggaaagca aatgctattt acagacctgc aagccctccc tcaaacnaaa ctatttctgg
 attaaatatg totgacttot tttgaggtca cacgactagg caaatgctat ttacgatctg
                                                                         180
 caaaagctgt ttgaagagtc aaagccccca tgtgaacacg atttctggac cctgtaacag
                                                                         240
                                                                         300
                                                                         301
        <210> 286
        <211> 301
        <212> DNA
       <213> Homo sapien
       <400> 286
 taccactgca ttccagcctg ggtgacagag tgagactccg tctccaaaaa aaactttgct
 tgtatattat ttttgcctta cagtggatca ttctagtagg aaaggacagt aagattttt
                                                                         60
 atcaaaatgt gtcatgccag taagagatgt tatattcttt tctcatttct tccccaccca
                                                                         120
 aaaataaget accatatage ttataageet caaatttttg cettttacta aaatgtgatt
                                                                        180
 gtttctgttc attgtgtatg cttcatcacc tatattaggc aaattccatt ttttcccttg
                                                                        240
                                                                        300
                                                                        301
       <210> 287
       <211> 301
       <212> DNA
       <213> Homo sapien
       <400> 287
tacagatctg ggaactaaat attaaaaatg agtgtggctg gatatatgga gaatgttggg
cccagaagga acgtagagat cagatattac aacagctttg ttttgagggt tagaaatatg
                                                                         60
aaatgatttg gttatgaacg cacagtttag gcagcagggc cagaatcctg accetetgcc
                                                                        120
ccgtggttat ctcctcccca gcttggctgc ctcatgttat cacagtattc cattttgttt
                                                                        180
gttgcatgtc ttgtgaagcc atcaagattt tctcgtctgt tttcctctca ttggtaatgc
                                                                        240
                                                                        300
                                                                        301
      <210> 288
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 288
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agtcaatagg aagacaaatt ccagttccag ctcagtctgg gtatctgcaa agctgcaaaa
                                                                        60
gatetttaaa gacaatttea agagaatatt teettaaagt tggcaatttg gagateatae
                                                                       120
aaaagcatct gcttttgtga tttaatttag ctcatctggc cactggaaga atccaaacag
                                                                       180
tctgccttaa ttttggatga atgcatgatg gaaattcaat aatttagaaa gttaaaaaaa
                                                                       240
                                                                       300
                                                                       301
      <210> 289
      <211> 301
      <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1) ... (301)
     <223> n = A,T,C \text{ or } G
     <400> 289
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ggtacactgt ttccatgtta tgtttctaca cattgctacc tcagtgctcc tggaaactta
                                                                          60
gcttttgatg tctccaagta gtccaccttc atttaactct ttgaaactgt atcatctttg
                                                                         120
ccaagtaaga gtggtggcct atttcagctg ctttgacaaa atgactggct cctgacttaa
                                                                         180
cgttctataa atgaatgtgc tgaagcaaag tgcccatggt ggcggcgaan aagagaaaga
                                                                         240
tgtgttttgt tttggactct ctgtggtccc ttccaatgct gtgggtttcc aaccagngga
                                                                         300
a
                                                                         301
       <210> 290
       <211> 301
       <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(301)
      <223> n = A, T, C \text{ or } G
      <400> 290
acactgaget ettettgata aatatacaga atgettggea tatacaagat tetatactae
                                                                         60
tgactgatct gttcatttct ctcacagctc ttacccccaa aagcttttcc accctaagtg
                                                                        120
ttctgacctc cttttctaat cacagtaggg atagaggcag anccacctac aatgaacatg
                                                                        180
gagttetate aagaggeaga aacageaeag aateceagtt ttaceatteg etageagtge
                                                                        240
tgccttgaac aaaaacattt ctccatgtct cattttcttc atgcctcaag taacagtgag
                                                                        300
                                                                        301
      <210> 291
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 291
caggtaccaa tttcttctat cctagaaaca tttcatttta tgttgttgaa acataacaac
                                                                         60
tatatcagct agatttttt tctatgcttt acctgctatg gaaaatttga cacattctgc
                                                                        120
tttactcttt tgtttatagg tgaatcacaa aatgtatttt tatgtattct gtagttcaat
                                                                        180
agccatggct gtttacttca tttaatttat ttagcataaa gacattatga aaaggcctaa
                                                                        240
acatgagett caetteecca ctaactaatt ageatetgtt atttettaac egtaatgeet
                                                                        300
                                                                        301
      <210> 292
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(301)
      <223> n = A, T, C \text{ or } G
      <400> 292
accttttagt agtaatgtct aataataaat aagaaatcaa ttttataagg tccatatagc
                                                                         60
tgtattaaat aatttttaag tttaaaagat aaaataccat cattttaaat gttggtattc
                                                                        120
aaaaccaaag natataaccg aaaggaaaaa cagatgagac ataaaatgat ttgcnagatg
                                                                        180
ggaaatatag tasttyatga atgttnatta aattccagtt ataatagtgg ctacacactc
                                                                       240
tcactacaca cacagacccc acagtcctat atgccacaaa cacatttcca taacttgaaa
                                                                       300
                                                                        301
```

```
<210> 293
        <211> 301
        <212> DNA
        <213> Homo sapien
        <400> 293
  ggtaccaagt gctggtgcca gcctgttacc tgttctcact gaaaagtctg gctaatgctc
  ttgtgtagtc acttctgatt ctgacaatca atcaatcaat ggcctagagc actgactgtt
                                                                       60
  aacacaaacg tcactagcaa agtagcaaca gctttaagtc taaatacaaa gctgttctgt
                                                                      120
  gtgagaattt tttaaaaggc tacttgtata ataacccttg tcatttttaa tgtacctcgg
                                                                      180
  ccgcgaccac gctaagccga attctgcaga tatccatcac actggcggcc gctcgagcat
                                                                      240
                                                                      300
                                                                      301
       <210> 294
       <211> 301
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(301)
       <223> n = A,T,C or G
       <400> 294
 tgacccataa caatatacac tagctatctt tttaactgtc catcattagc accaatgaag
 attcaataaa attaccttta ttcacacatc tcaaaacaat tctgcaaatt cttagtgaag
                                                                      60
 tttaactata gtcacaganc ttaaatattc acattgtttt ctatgtctac tgaaaataag
                                                                     120
 ttcactactt ttctgggata ttctttacaa aatcttatta aaattcctgg tattatcacc
                                                                     180
 cccaattata cagtagcaca accaccttat gtagttttta catgatagct ctgtagaggt
                                                                     240
                                                                     300
                                                                     301
       <210> 295
      <211> 305
      <212> DNA
      <213> Homo sapien
      <400> 295
gtactctttc tctcccctcc tctgaattta attctttcaa cttgcaattt gcaaggatta
60
ttggtttgtg aatccatctt gctttttccc cattggaact agtcattaac ccatctctga
                                                                    120
actggtagaa aaacrtctga agagctagtc tatcagcatc tgacaggtga attggatggt
                                                                    180
tetcagaacc atttcaccca gacageetgt ttetateetg tttaataaat tagtttgggt
                                                                    240
                                                                    300
                                                                    305
      <210> 296
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 296
aggtactatg ggaagctgct aaaataatat ttgatagtaa aagtatgtaa tgtgctatct
cacctagtag taaactaaaa ataaactgaa actttatgga atctgaagtt attttccttg
                                                                    60
attaaataga attaataaac caatagagg aaacatgaaa ccatgcaatc tactatcaac
                                                                    120
tttgaaaaag tgattgaacg aaccacttag ctttcagatg atgaacactg ataagtcatt
                                                                   180
                                                                   240
```

```
tgtcattact ataaatttta aaatctgtta ataagatggc ctatagggag gaaaaagggg
                                                                         300
 С
                                                                         301
       <210> 297
       <211> 300
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(300)
       <223> n = A,T,C \text{ or } G
       <400> 297
actgagtttt aactggacgc caagcaggca aggctggaag gttttgctct ctttgtgcta
                                                                          60
aaggttttga aaaccttgaa ggagaatcat tttgacaaga agtacttaag agtctagaga
                                                                         120
acaaagangt gaaccagctg aaagctctcg ggggaanctt acatgtgttg ttaggcctgt
                                                                         180
tccatcattg ggagtgcact ggccatccct caaaatttgt ctgggctggc ctgagtggtc
                                                                         240
accgcacctc ggccgcgacc acgctaagcc gaattctgca gatatccatc acactggcgg
                                                                         300
       <210> 298
       <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(301)
      \langle 223 \rangle n = A,T,C or G
      <400> 298
tatggggttt gtcacccaaa agctgatgct gagaaaggcc tccctggggc ccctcccgcg
                                                                         60
ggcatctgag agacctggtg ttccagtgtt tctggaaatg ggtcccagtg ccgccggctg
                                                                        120
tgaagetete agateaatea egggaaggge etggeggtgg tggeeacetg gaaceacet
                                                                        180
gtcctgtctg tttacatttc actaycaggt tttctctggg cattacnatt tgttccccta
                                                                        240
caacagtgac ctgtgcattc tgctgtggcc tgctgtgtct gcaggtggct ctcagcgagg
                                                                        300
                                                                        301
      <210> 299
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 299
gttttgagac ggagtttcac tcttgttgcc cagactggac tgcaatggca gggtctctgc
                                                                         60
teactgcace etetgcetee caggttegag caatteteet geeteageet eccaggtage
                                                                        120
tgggattgca ggctcacgcc accataccca gctaattttt ttgtattttt agtagagacg
                                                                        180
gagtttcgcc atgttggcca gctggtctca aactcctgac ctcaagcgac ctgcctgcct
                                                                        240
cggcctccca aagtgctgga attataggca tgagtcaaca cgcccagcct aaagatattt
                                                                        300
                                                                        301
      <210> 300
      <211> 301
      <212> DNA
      <213> Homo sapien
```

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<400> 300
  attcagtttt atttgctgcc ccagtatctg taaccaggag tgccacaaaa tcttgccaga
  tatgtcccac acccactggg aaaggctccc acctggctac ttcctctatc agctgggtca
                                                                          60
  gctgcattcc acaaggttct cagcctaatg agtttcacta cctgccagtc tcaaaactta
                                                                         120
  gtaaagcaag accatgacat tcccccacgg aaatcagagt ttgccccacc gtcttgttac
                                                                         180
  tataaageet geetetaaca greerrgett erreacacea arecegageg careeceear
                                                                         240
                                                                         300
                                                                         301
        <210> 301
        <211> 301
        <212> DNA
        <213> Homo sapien
        <400> 301
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 agaggacccc aggtctccaa gcaaccacat ggtcaagggc atgaataatt aaaagttggt
                                                                         60
 gggaactcac aaagaccctc agagctgaga cacccacaac agtgggagct cacaaagacc
                                                                        120
 ctcagagctg agacacccac aacagtggga gctcacaaag accctcagag ctgagacacc
                                                                        180
 cacaacagca cctcgttcag ctgccacatg tgtgaataag gatgcaatgt ccagaagtgt
                                                                        240
                                                                        300
                                                                        301
       <210> 302
       <211> 301
       <212> DNA
       <213> Homo sapien
       <400> 302
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 tgaattttga aaattactac ttaatcctaa ttcacaataa caatggcatt aaggtttgac
                                                                        60
 ttgagttggt tcttagtatt atttatggta aataggctct taccacttgc aaataactgg
                                                                       120
ccacatcatt aatgactgac ttcccagtaa ggctctctaa ggggtaagta ggaggatcca
                                                                       180
caggatttga gatgctaagg ccccagagat cgtttgatcc aaccctctta ttttcagagg
                                                                       240
                                                                       300
g
                                                                       301
       <210> 303
       <211> 301
       <212> DNA
       <213> Homo sapien
       <400> 303
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atattgtttt ttgacagttt aacacatctt cttctgtcag agattctttc acaatagcac
                                                                        60
tggctaatgg aactaccgct tgcatgttaa aaatggtggt ttgtgaaatg atcataggcc
                                                                       120
agtaacgggt atgttttct aactgatctt ttgctcgttc caaagggacc tcaagacttc
                                                                       180
catcgatttt atatctgggg tctagaaaag gagttaatct gttttccctc ataaattcac
                                                                       240
                                                                       300
                                                                       301
      <210> 304
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 304
acatggatgt tattttgcag actgtcaacc tgaatttgta tttgcttgac attgcctaat
                                                                       60
```

<213> Homo sapien

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tattagtttc agtttcagct tacccacttt ttgtctgcaa catgcaraas agacagtgcc
                                                                        120
 ctttttagtg tatcatatca ggaatcatct cacattggtt tgtgccatta ctggtgcagt
                                                                        180
 gactttcagc cacttgggta aggtggagtt ggccatatgt ctccactgca aaattactga
                                                                        240
 ttttcctttt gtaattaata agtgtgtgtg tgaagattct ttgagatgag gtatatatct
                                                                        300
                                                                        301
       <210> 305
       <211> 301
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(301)
       <223> n = A, T, C or G
      <400> 305
gangtacagc gtggtcaagg taacaagaag aaaaaaatgt gagtggcatc ctgggatgag
                                                                        60
cagggggaca gacctggaca gacacgttgt catttgctgc tgtgggtagg aaaatgggcg
                                                                       120
taaaggagga gaaacagata caaaatctcc aactcagtat taaggtattc tcatgcctag
                                                                       180
aatattggta gaaacaagaa tacattcata tggcaaataa ctaaccatgg tggaacaaaa
                                                                       240
ttctgggatt taagttggat accaangaaa ttgtattaaa agagctgttc atggaataag
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                                                                       301
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      <400> 306
Val Leu Gly Trp Val Ala Glu Leu
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      <211> 637
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      <400> 307
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                                                                       120
attgaggaat gatacttgag cccaaagagc attcaatcat tgttttattt gccttmtttt
                                                                       180
cacaccattg gtgagggagg gattaccacc ctggggttat gaagatggtt gaacacccca
                                                                       240
cacatagcac cggagatatg agatcaacag tttcttagcc atagagattc acagcccaga
                                                                       300
gcaggaggac gcttgcacac catgcaggat gacatggggg atgcgctcgg gattggtgtg
                                                                       360
aagaagcaag gactgttaga ggcaggcttt atagtaacaa gacggtgggg caaactctga
                                                                       420
tttccgtggg ggaatgtcat ggtcttgctt tactaagttt tgagactggc aggtagtgaa
                                                                      480
actcattagg ctgagaacct tgtggaatgc acttgaccca sctgatagag gaagtagcca
                                                                      540
ggtgggagcc tttcccagtg ggtgtgggac atatctggca agattttgtg gcactcctgg
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                                                                      637
     <210> 308
     <211> 647
     <212> DNA
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  tgctcagggg aaggttcata tgggactttc tactgcccaa ggttctatac aggatataaa
                                                                          60
  ggngcctcac agtatagatc tggtagcaaa gaagaagaaa caaacactga tctctttctg
                                                                         120
 ccacccctct gaccctttgg aactcctctg accctttaga acaagcctac ctaatatctg
                                                                         180
 ctagagaaaa gaccaacaac ggcctcaaag gatctcttac catgaaggtc tcagctaatt
                                                                         240
 cttggctaag atgtgggttc cacattaggt tctgaatatg gggggaaggg tcaatttgct
                                                                         300
 cattttgtgt gtggataaag tcaggatgcc caggggccag agcagggggc tgcttgcttt
                                                                         360
 gggaacaatg gctgagcata taaccatagg ttatggggaa caaaacaaca tcaaagtcac
                                                                         420
 tgtatcaatt gccatgaaga cttgagggac ctgaatctac cgattcatct taaggcagca
                                                                         480
 ggaccagttt gagtggcaac aatgcagcag cagaatcaat ggaaacaaca gaatgattgc
                                                                         540
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                                                                         600
                                                                         647
       <210> 309
       <211> 460
       <212> DNA
       <213> Homo sapien
       <400> 309
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 aatatgattg gctgcacact tccagactga tgaatgatga acgtgatgga ctattgtatg
                                                                         60
 gagcacatct tcagcaagag ggggaaatac tcatcatttt tggccagcag ttgtttgatc
                                                                        120
 accaaacatc atgccagaat actcagcaaa ccttcttagc tcttgagaag tcaaagtccg
                                                                        180
ggggaattta ttcctggcaa ttttaattgg actccttatg tgagagcagc ggctacccag
                                                                        240
ctggggtggt ggagcgaacc cgtcactagt ggacatgcag tggcagagct cctggtaacc
                                                                        300
acctagagga atacacaggc acatgtgtga tgccaagcgt gacacctgta gcactcaaat
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ttgtcttgtt tttgtctttc ggtgtgtaag attcttaagt
                                                                        420
                                                                        460
       <210> 310
       <211> 539
       <212> DNA
      <213> Homo sapien
      <400> 310
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ctaaaggttt taaaatatgt caggattgga agaaggcatg gataaagaac aaagttcagt
                                                                        60
taggaaagag aaacacagaa ggaagagaca caataaaagt cattatgtat tctgtgagaa
                                                                       120
greagaeagt aagattigig ggaaatgggt tggttigitg tatggtaigt attitageaa
                                                                       180
taatetttat ggeagagaaa getaaaatee tttagettge gtgaatgate aettgetgaa
                                                                       240
ttcctcaagg taggcatgat gaaggaggt ttagaggaga cacagacaca atgaactgac
                                                                       300
ctagatagaa agccttagta tactcagcta ggaatagtga ttctgagggc acactgtgac
                                                                       360
atgattatgt cattacatgt atggtagtga tggggatgat aggaaggaag aacttatggc
                                                                       420
atattttcac ccccacaaaa gtcagttaaa tattgggaca ctaaccatcc aggtcaaga
                                                                       480
                                                                       539
      <210> 311
      <211> 526
      <212> DNA
      <213> Homo sapien
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                                                                        120
 catttacagc atttaaaatg tgttcagcat gaaatattag ctacagggga agctaaataa
                                                                        180
 attaaacatg gaataaagat ttgtccttaa atataatcta caagaagact ttgatatttg
                                                                        240
 tttttcacaa gtgaagcatt cttataaagt gtcataacct ttttggggaa actatgggaa
 aaaatgggga aactctgaag ggttttaagt atcttacctg aagctacaga ctccataacc
                                                                        300
                                                                        360
 tetetttaca gggageteet geageeeeta cagaaatgag tggetgagat tettgattge
                                                                        420
 acagcaagag cttctcatct aaaccctttc cctttttagt atctgtgtat caagtataaa
                                                                        480
 agttctataa actgtagtnt acttatttta atccccaaag cacagt
                                                                        526
       <210> 312
       <211> 500
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1) ... (500)
       <223> n = A,T,C \text{ or } G
       <400> 312
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                                                                       120
ccatttctct ttcccttcca cctgccagtt ttgctgactc tcaacttgtc atgagtgtaa
                                                                       180
gcattaagga cattatgctt cttcgattct gaagacaggc cctgctcatg gatgactctg
gcttcttagg aaaatattt tcttccaaaa tcagtaggaa atctaaactt atcccctctt
                                                                       240
                                                                       300
tgcagatgtc tagcagcttc agacatttgg ttaagaaccc atgggaaaaa aaaaaatcct
                                                                       360
tgctaatgtg gtttcctttg taaaccanga ttcttatttg nctggtatag aatatcagct
                                                                       420
ctgaacgtgt ggtaaagatt tttgtgtttg aatataggag aaatcagttt gctgaaaagt
                                                                       480
tagtcttaat tatctattgg
                                                                       500
      <210> 313
      <211> 718
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(718)
      <223> n = A,T,C or G
      <400> 313
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ctgctgaaat ggagataatt aacatcacta gaaacagcaa gatgacaata taatgtctaa
                                                                       120
                                                                      180
gtagtgacat gtttttgcac atttccagcc cttttaaata tccacacaca caggaagcac
                                                                      240
aaaaggaagc acagagatcc ctgggagaaa tgcccggccg ccatcttggg tcatcgatga
                                                                      300
gcctcgccct gtgcctgntc ccgcttgtga gggaaggaca ttagaaaatg aattgatgtg
                                                                      360
ttccttaaag gatggcagga aaacagatcc tgttgtggat atttatttga acgggattac
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agatttgaaa tgaagtcaca aagtgagcat taccaatgag aggaaaacag acgagaaaat cttgatggtt cacaagacat gcaacaaca aaatggaata ctgtgatgac acgagcagcc aactggggag gagataccac ggggcagagg tcaggattct ggccctgctg cctaactgtg ttcttntggc ccacattttc atnatccacc ccntcntttt aannttantc caaantgt	480 540 600 660 718
<pre>&lt;400&gt; 314 gtttatttac attacagaaa aaacatcaag acaatgtata ctatttcaaa tatatccata cataatcaaa tatagctgta gtacatgttt tcattggtgt agattaccac aaatgcaagg caacatgtgt agatctcttg tcttattctt ttgtctataa tactgtattg tgtagtccaa gctctcggta gtccagccac tgtgaaacat gctcccttta gattaacctc gtggacgctc tctggggcat ttccttgtga tgcagaggac caccacacag atgacagcaa tctgaatt </pre> <pre>&lt;210&gt; 315</pre> <pre>&lt;211&gt; 341</pre>	60 120 180 240 300 358
<pre>&lt;212&gt; DNA &lt;213&gt; Homo sapien  &lt;400&gt; 315  taccacctcc ccgctggcac tgatgagccg catcaccatg gtcaccagca ccatgaaggc ataggtgatg atgaggacat ggaatgggcc cccaaggatg gtctgtccaa agaagcgagt gacccccatt ctgaagatgt ctggaacctc taccagcagg atgatgatag ccccaatgac agtcaccagc tccccgacca gccggatatc gtccttaggg gtcatgtagg cttcctgaag tagcttctgc tgtaagaggg tgttgtcccg ggggctcgtg cggttattgg tcctgggctt gagggggcgg tagatgcagc acatggtgaa gcagatgatg t</pre>	60 120 180 240 300 341
<pre>&lt;210&gt; 316   &lt;211&gt; 151   &lt;212&gt; DNA   &lt;213&gt; Homo sapien  &lt;400&gt; 316 agactgggca agactcttac gccccacact gcaatttggt cttgttgccg tatccattta tgtgggcctt tctcgagttt ctgattataa acaccactgg agcgatgtgt tgactggact cattcaggga gctctggttg caatattagt t</pre>	60 120 151
<210> 317	60 120 151
<211> 151 <212> DNA	

<213> Homo sapien <400> 318 actggtggga ggcgctgttt agttggctgt tttcagaggg gtctttcgga gggacctcct 60 gctgcaggct ggagtgtctt tattcctggc gggagaccgc acattccact gctgaggctg 120 tgggggggt ttatcaggca gtgataaaca t 151 <210> 319 <211> 151 <212> DNA <213> Homo sapien <400> 319 aactagtgga tccagagcta taggtacagt gtgatctcag ctttgcaaac acattttcta 60 catagatagt actaggtatt aatagatatg taaagaaaga aatcacacca ttaataatgg 120 taagattggg tttatgtgat tttagtgggt a 151 <210> 320 <211> 150 <212> DNA <213> Homo sapien <400> 320 aactagtgga tccactagtc cagtgtggtg gaattccatt gtgttggggt tctagatcgc 60 gageggetge cerrittit trittitit ggggggaart trittitit aaragttatt 120 gagtgttcta cagcttacag taaataccat 150 <210> 321 <211> 151 <212> DNA <213> Homo sapien <400> 321 agcaactttg tttttcatcc aggttatttt aggcttagga tttcctctca cactgcagtt 60 tagggtggca ttgtaaccag ctatggcata ggtgttaacc aaaggctgag taaacatggg 120 tgcctctgag aaatcaaagt cttcatacac t 151 <210> 322 <211> 151 <212> DNA <213> Homo sapien <220> <221> misc\_feature <222> (1)...(151) <223> n = A, T, C or G<400> 322 atccagcate ttetectgtt tettgeette ettttette ttettasatt etgettgagg 60 tttgggcttg gtcagtttgc cacagggctt ggagatggtg acagtcttct ggcattcggc 120 attgtgcagg gctcgcttca nacttccagt t 151 <210> 323 <211> 151 <212> DNA

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         <222> (1)...(151)
         <223> n = A,T,C or G
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  nagactcant tactacccag trtgrggttt twtgggagaa atgtaactgg acagttagct
                                                                           60
  gttcaatyaa aaagacactt ancccatgtg g
                                                                          120
                                                                          151
        <210> 324
        <211> 461
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc_feature
        <222> (1)...(461)
        <223> n = A, T, C \text{ or } G
        <400> 324
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 agaagtggtc agctaaagga atccaggttg ttggttggac tgttaatacc tttgatgaaa
                                                                          60
 agagttacta cgaatcccat cttggttcca gctatatcac tgacagcatg gtagaagact
                                                                         120
 gcgaacctca cttctagact ttcacggtgg gacgaaacgg gttcagaaac tgccaggggc
                                                                         180
 ctcatacagg gatatcaaaa taccetttgt getacceagg ceetggggaa teaggtgact
                                                                         240
 cacacaaatg caatagttgg tcactgcatt tttacctgaa ccaaagctaa acccggtgtt
                                                                         300
 gccaccatgc accatggcat gccagagttc aacactgttg ctcttgaaaa ttgggtctga
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 aaaaacgcac aagagcccct gccctgccct agctgangca c
                                                                         420
                                                                         461
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       <211> 400
       <212> DNA
       <213> Homo sapien
       <400> 325
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tttgatgtct ccaagtagtc caccttcatt taactctttg aaactgtatc atctttgcca
                                                                         60
agtaagagtg gtggcctatt tcagctgctt tgacaaaatg actggctcct gacttaacgt
                                                                        120
tctataaatg aatgtgctga agcaaagtgc ccatggtggc ggcgaagaag agaaagatgt
                                                                        180
gttttgtttt ggactctctg tggtcccttc caatgctgtg ggtttccaac caggggaagg
                                                                        240
gtcccttttg cattgccaag tgccataacc atgagcacta cgctaccatg gttctgcctc
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                                                                        400
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      <211> 1215
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                                                                        60
gaactcctac accatcgggc tgggcctgca cagtcttgag gccgaccaag agccagggag
                                                                       120
                                                                       180
```

300

360

420

480

540

600

660

720

780

840

900

960 1020

1080

1140

1200

1215

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               5
                                   10
Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val
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Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly
                           40
Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu
                                          60
Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu Ala
                                      75
Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp
               85
                                  90
Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn
           100
                               105
Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met Pro
                           120
                                              125
Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu Val Cys
                       135
                                          140
Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala Gly
                   150
                                      155
Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly Pro
                                  170
Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys Ala
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185

Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu Cys Lys 200

Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser

215

190

<210> 328

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<211> 234
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                                                                        180
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       <400> 329
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 1
                 5
                                     10
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 Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val Leu Ser Ala Thr
                             40
 His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu
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                                             60
 Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu Ala
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gctgcaqcca
                                                                       70
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      <211> 22
      <212> PRT
      <213> Homo sapien
      <400> 331
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                5
                                   10
Val Ser Gly Ser Cys Ser
            20
      <210> 332
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                                                                       60
                                                                      120
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gtacatcaac tgttcagctt cctgggaaag tagttgtggt cacaggagct aatacaggta
                                                                       180
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 gggatgtgga aaagggggaa ttggtggcca aagagatcca gaccacgaca gggaaccagc
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                                                                       300
                                                                       360
 gettettage tgaggaaaag cacetecaeg ttttgateaa caatgeagga gtgatgatgt
                                                                       420
 gtccgtactc gaagacagca gatggctttg agatgcacat aggagtcaac cacttgggtc
                                                                       480
 acttcctcct aacccatctg ctgctagaga aactaaagga atcagcccca tcaaggatag
                                                                       540
 taaatgtgtc ttccctcgca catcacctgg gaaggatcca cttccataac ctgcagggcg
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                                                                       960
                                                                      1020
 ctacacagta cttcttgtca aaatgattct ccttcaaggt tttcaaaacc tttagcacaa
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 agagagcaaa accttccagc cttgcctgct tggtgtccag ttaaaactca gtgtactgcc
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 agattcgtct aaatgtctgt catgtccaga tttactttgc ttctgttact gccagagtta
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 gaactagett etttgtteac aatteagtte eteceaacea accagtette aetteaagag
                                                                     1320
                                                                     1380
 ggccacactg caacctcagc ttaacatgaa taacaaagac tggctcagga gcagggcttg
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WO 00/04149 PCT/US99/15838

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                                                                       300
ggggtagttg gaagggactg aaattgtggg gggaaggtag gaggcacatc aataaagagg
                                                                       360
aaaccaccaa gctgaaaaaa aa
                                                                       382
      <210> 344
      <211> 536
      <212> DNA
      <213> Homo sapien
      <400> 344
ctgggcctga agctgtaggg taaatcagag gcaggcttct gagtgatgag agtcctgaga
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caataggcca cataaacttg gctggatgga acctcacaat aaggtggtca cctcttgttt
                                                                       120
gtttaggggg atgccaagga taaggccagc tcagttatat gaagagaagc agaacaaaca
                                                                       180
agtettteag agaaatggat geaateagag tgggateeeg gteacateaa ggteacaete
                                                                       240
caccttcatg tgcctgaatg gttgccaggt cagaaaaatc cacccttac gagtgcggct
                                                                       300
togaccotat atococogoo ogogtocott totocataaa attottotta gtagotatta
                                                                       360
ccttcttatt atttgatcta gaaattgccc tccttttacc cctaccatga gccctacaaa
                                                                       420
caactaacct gccactaata gttatgtcat ccctcttatt aatcatcatc ctagccctaa
                                                                       480
gtctggccta tgagtgacta caaaaaggat tagactgagc cgaataacaa aaaaaa
                                                                       536
      <210> 345
      <211> 251
      <212> DNA
      <213> Homo sapien
      <400> 345
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tgaatgaagc ccccatcttt gtgcctcctg aaaagagagt ggaagtgtcc gaggactttg
                                                                      120
gcgtgggcca ggaaatcaca tcctacactg cccaggagcc agacacattt atggaacaga
                                                                      180
aaataacata tcggatttgg agagacactg ccaactggct ggagattaat ccggacactg
                                                                      240
gtgccatttc c
                                                                      251
```

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<210> 346
         <211> 282
         <212> DNA
         <213> Homo sapien
         <220>
         <221> misc_feature
         <222> (1)...(282)
         <223> n = A, T, C or G
  <400> 346
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  ctaagtcttg ttaccaaaaa aaggaaaaag aaaagatctt ctcagttaca aattctggga
                                                                          60
  agggagacta tacctggctc ttgccctaag tgagaggtct tccctcccgc accaaaaaat
                                                                         120
  agaaaggctt tctatttcac tggcccaggt agggggaagg agagtaactt tgagtctgtg
                                                                         180
  ggtctcattt cccaaggtgc cttcaatgct catnaaaacc aa
                                                                         240
                                                                         282
        <210> 347
        <211> 201
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc_feature
        <222> (1)...(201)
        <223> n = A, T, C or G
        <400> 347
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 taaatataac ttttaaaana ntactancag cttttaccta ngctcctaaa tgcttgtaaa
                                                                         60
 tetgagaetg aetggaecca eccagaecca gggeaaagat acatgttace atateatett
                                                                        120
 tataaagaat tttttttgt c
                                                                        180
                                                                        201
       <210> 348
       <211> 251
       <212> DNA
       <213> Homo sapien
       <400> 348
ctgttaatca caacatttgt gcatcacttg tgccaagtga gaaaatgttc taaaatcaca
agagagaaca gtgccagaat gaaactgacc ctaagtccca ggtgcccctg ggcaggcaga
                                                                        60
aggagacact cccagcatgg aggagggttt atctttcat cctaggtcag gtctacaatg
                                                                       120
ggggaaggtt ttattataga actcccaaca gcccacctca ctcctgccac ccacccgatg
                                                                       180
gccctgcctc c
                                                                       240
                                                                       251
      <210> 349
      <211> 251
      <212> DNA
      <213> Homo sapien
      <400> 349
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aacccctgag gatgccagag ctatgggtcc agaacatggt gtggtattat caacagagtt
                                                                       60
cagaagggtc tgaactctac gtgttaccag agaacataat gcaattcatg cattccactt
                                                                      120
agcaattttg taaaatacca gaaacagacc ccaagagtct ttcaagatga ggaaaattca
                                                                      180
                                                                      240
```

```
actcctggtt t
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        <210> 350
        <211> 908
        <212> DNA
        <213> Homo sapien
        <400> 350
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 agecegeeg gtgaageteg etgettteee taceteetta agtgaetgee aaacgeecae
                                                                         60
 eggetggaat tgetetggtt atgatgacag agaaaatgat etetteetet gtgacaccaa
                                                                        120
 cacctgtaaa tttgatgggg aatgtttaag aattggagac actgtgactt gcgtctgtca
                                                                        180
 gttcaagtgc aacaatgact atgtgcctgt gtgtggctcc aatggggaga gctaccagaa
                                                                        240
 tgagtgttac ctgcgacagg ctgcatgcaa acagcagagt gagatacttg tggtgtcaga
                                                                        300
 aggatcatgt gccacagtcc atgaaggctc tggagaaact agtcaaaagg agacatccac
                                                                        360
 ctgtgatatt tgccagtttg gtgcagaatg tgacgaagat gccgaggatg tctggtgtgt
                                                                        420
 gtgtaatatt gactgttete aaaccaactt caateceete tgegettetg atgggaaate
                                                                        480
 ttatgataat gcatgccaaa tcaaagaagc atcgtgtcag aaacaggaga aaattgaagt
                                                                        540
 catgiciting ggicgatgic aagataacac aactacaact actaagicin aagatgggca
                                                                        600
 ttatgcaaga acagattatg cagagaatgc taacaaatta gaagaaagtg ccagagaaca
                                                                        660
 ccacatacct tgtccggaac attacaatgg cttctgcatg catgggaagt gtgagcattc
                                                                        720
 tatcaatatg caggagccat cttgcaggtg tgatgctggt tatactggac aacactgtga
                                                                        780
 aaaaaaggac tacagtgttc tatacgttgt tcccggtcct gtacgatttc agtatgtctt
                                                                        840
                                                                        900
 aatcgcag
                                                                        908
       <210> 351
       <211> 472
       <212> DNA
       <213> Homo sapien
       <400> 351
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gtcaaacctt aatgccattg ttattgtgaa ttaggattaa gtagtaattt tcaaaattca
                                                                        60
cattaacttg attttaaaat cagwtttgyg agtcatttac cacaagctaa atgtgtacac
                                                                       120
tatgataaaa acaaccattg tattcctgtt tttctaaaca gtcctaattt ctaacactgt
                                                                       180
atatatcctt cgacatcaat gaactttgtt ttcttttact ccagtaataa agtaggcaca
                                                                       240
gatctgtcca caacaaactt gccttctcat gccttgcctc tcaccatgct ctgctccagg
                                                                       300
teageceet titiggeetgt tigttitgte aaaaacetaa tetgettett gettitettg
                                                                       360
gtaatatata tttagggaag atgttgcttt gcccacacac gaagcaaagt aa
                                                                       420
                                                                       472
      <210> 352
      <211> 251
      <212> DNA
      <213> Homo sapien
      <400> 352
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tgtggataag gccaggtcaa tggctgcaag catgcagaga aagaggtaca tcggagcgtg
                                                                       60
caggetgegt teegteetta egatgaagae caegatgeag tttecaaaca ttgccaetae
                                                                      120
atacatggaa aggagggga agccaaccca gaaatgggct ttctctaatc ctgggatacc
                                                                      180
                                                                      240
aataagcaca a
                                                                      251
      <210> 353
      <211> 436
      <212> DNA
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```
<213> Homo sapien
```

```
<400> 353
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   cacattatgg tattattact atactgatta tatttatcat gtgacttcta attaraaaat
                                                                          60
  gtatccaaaa gcaaaacagc agatatacaa aattaaagag acagaagata gacattaaca
                                                                         120
  gataaggcaa cttatacatt gacaatccaa atccaataca tttaaacatt tgggaaatga
                                                                         180
  gggggacaaa tggaagccar atcaaatttg tgtaaaacta ttcagtatgt ttcccttgct
                                                                         240
  tcatgtctga raaggctctc ccttcaatgg ggatgacaaa ctccaaatgc cacacaaatg
                                                                         300
  ttaacagaat actagattca cactggaacg ggggtaaaga agaaattatt ttctataaaa
                                                                         360
  gggctcctaa tgtagt
                                                                         420
                                                                         436
        <210> 354
        <211> 854
        <212> DNA
        <213> Homo sapien
        <400> 354
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 caagtetgaa accaaateta ggaaacatag gaaacgagee aggeacaggg etggtgggee
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 atcagggacc accetttggg ttgatatttt gettaatetg catettttga gtaagateat
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 ctggcagtag aagctgttct ccaggtacat ttctctagct catgtacaaa aacatcctga
                                                                        180
 aggactttgt caggtgcctt gctaaaagcc agatgcgttc ggcacttcct tggtctgagg
                                                                        240
 ttaattgcac acctacagge actgggetea tgetttcaag tattttgtee teactttagg
                                                                        300
 gtgagtgaaa gatccccatt ataggagcac ttgggagaga tcatataaaa gctgactctt
                                                                        360
 gagtacatgc agtaatgggg tagatgtgtg tggtgtgtct tcattcctgc aagggtgctt
                                                                        420
 gttagggagt gtttccagga ggaacaagtc tgaaaccaat catgaaataa atggtaggtg
                                                                        490
 tgaactggaa aactaattca aaagagagat cgtgatatca gtgtggttga tacaccttgg
                                                                        540
 caatatggaa ggctctaatt tgcccatatt tgaaataata attcagcttt ttgtaataca
                                                                        600
 aaataacaaa ggattgagaa tcatggtgtc taatgtataa aagacccagg aaacataaat
                                                                        550
 atatcaactg cataaatgta aaatgcatgt gacccaagaa ggccccaaag tggcagacaa
                                                                        720
 cattgtaccc attttccctt ccaaaatgtg agcggcgggc ctgctgcttt caaggctgtc
                                                                       780
                                                                       840
                                                                       854
       <210> 355
       <211> 676
       <212> DNA
       <213> Homo sapien
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caggtcaaag ctgatctttc tggaatgtca ccaaccaagg gcctatattt atcaaaagcc
                                                                        60
atccacaagt catacctgga tgtcagcgaa gagggcacgg aggcagcagc agccactggg
                                                                       120
gacagcatcg ctgtaaaaag cctaccaatg agagctcagt tcaaggcgaa ccaccccttc
                                                                       180
ctgttcttta taaggcacac tcataccaac acgatcctat tctgtggcaa gcttgcctct
                                                                       240
ccctaatcag atggggttga gtaaggctca gagttgcaga tgaggtgcag agacaatcct
                                                                       300
gtgactttcc cacggccaaa aagctgttca cacctcacgc acctctgtgc ctcagtttgc
                                                                       360
tcatctgcaa aataggtcta ggatttcttc caaccatttc atgagttgtg aagctaaggc
                                                                      420
tttgttaatc atggaaaaag gtagacttat gcagaaagcc tttctggctt tcttatctgt
                                                                      480
ggtgtctcat ttgagtgctg tccagtgaca tgatcaagtc aatgagtaaa attttaaggg
                                                                      540
attagatttt cttgacttgt atgtatctgt gagatcttga ataagtgacc tgacatctct
                                                                      600
gcttaaagaa aaccag
                                                                      660
                                                                      676
```

<210> 356 <211> 574

<212> DNA ...

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<213> Homo sapien
       <400> 356
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 catgtggcac ctgactggca tcaaaccaaa gttcgtaggc caacaaagat gggccactca
                                                                      120
 caagetteee attigtagat eteagtgeet atgagtatet gacacetgtt cetetetea
                                                                      180
 gtctcttagg gaggcttaaa tctgtctcag gtgtgctaag agtgccagcc caaggkggtc
 aaaagtccac aaaactgcag tctttgctgg gatagtaagc caagcagtgc ctggacagca
                                                                      240
                                                                      300
 gagttetttt ettgggeaac agataaccag acaggaetet aategtgete ttatteaaca
 ttettetgte tetgeetaga etggaataaa aageeaatet etetegtgge acagggaagg
                                                                      360
 420
                                                                      480
 gatagacggc acagggagct cttaggtcag cgctgctggt tggaggacat tcctgagtcc
                                                                      540
 agctttgcag cctttgtgca acagtacttt ccca
                                                                      574
       <210> 357
       <211> 393
       <212> DNA
       <213> Homo sapien
      <400> 357
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                                                                       60
taatatggkg kettgtteae tataettaaa aatgeaeeae teataaatat ttaatteage
                                                                     120
aagccacaac caaracttga ttttatcaac aaaaacccct aaatataaac ggsaaaaaag
                                                                     180
atagatataa ttattccagt ttttttaaaa cttaaaaarat attccattgc cgaattaara
araarataag tgttatatgg aaagaagggc attcaagcac actaaaraaa cctgaggkaa
                                                                     240
gcataatctg tacaaaatta aactgtcctt tttggcattt taacaaattt gcaacgktct
                                                                     300
                                                                     360
tttttttttt tttctgtttt tttttttt tac
                                                                     393
      <210> 358
      <211> 630
      <212> DNA
      <213> Homo sapien
      <400> 358
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                                                                      60
ttaatgttta taggaaaatg atgagtttat gacaaaggaa gtagatagtg ttttacaaga
gcatagagta gggaagctaa tccagcacag ggaggtcaca gagacatccc taaggaagtg
                                                                     120
gagtttaaac tgagagaagc aagtgcttaa actgaaggat gtgttgaaga agaagggaga
                                                                     180
                                                                     240
gtagaacaat ttgggcagag ggaaccttat agaccctaag gtgggaaggt tcaaagaact
                                                                     300
gaaagagagc tagaacagct ggagccgttc tccggtgtaa agaggagtca aagagataag
attaaagatg tgaagattaa gatcttggtg gcattcaggg attggcactt ctacaagaaa
                                                                     360
                                                                     420
tcactgaagg gagtaatgtg acattacttt tcacttcagg atggccattc taactccagg
                                                                     480
gggtagactg gactaggtaa gactggaggc aggtagacct cttctaaggc ctgcgatagt
                                                                     540
gaaagacaaa aataagtggg gaaattcagg ggatagtgaa aatcagtagg acttaatgag
                                                                     600
caagccagag gttcctccac aacaaccagt
                                                                     630
      <210> 359
      <211> 620
      <212> DNA
      <213> Homo sapien
      <400> 359
acagcattcc aaaatataca tctagagact aarrgtaaat gctctatagt gaagaagtaa
taattaaaaa atgctactaa tatagaaaat ttataatcag aaaaataaat attcagggag
                                                                     60
                                                                    120
```

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ctcaccagaa gaataaagtg ctctgccagt tattaaagga ttactgctgg tgaattaaat
   atggcattcc ccaagggaaa tagagagatt cttctggatt atgttcaata tttatttcac
                                                                          180
   aggattaact gttttaggaa cagatataaa gcttcgccac ggaagagatg gacaaagcac
                                                                          240
   aaagacaaca tgatacctta ggaagcaaca ctaccctttc aggcataaaa tttggagaaa
                                                                          300
   tgcaacatta tgcttcatga ataatatgta gaaagaaggt ctgatgaaaa tgacatcctt
                                                                          360
   aatgtaagat aactttataa gaattctggg tcaaataaaa ttctttgaag aaaacatcca
                                                                         420
   aatgtcattg acttatcaaa tactatcttg gcatataacc tatgaaggca aaactaaaca
                                                                         480
  aacaaaaagc tcacaccaaa caaaaccatc aacttatttt gtattctata acatacgaga
                                                                         540
  ctgtaaagat gtgacagtgt
                                                                         600
                                                                         620
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        <211> 431
        <212> DNA
        <213> Homo sapien
        <400> 360
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  tgatgaatga tgaacgtgat ggactattgt atggagcaca tcttcagcaa gagggggaaa
                                                                         60
  tactcatcat ttttggccag cagttgtttg atcaccaaac atcatgccag aatactcage
                                                                         120
  aaaccttctt agctcttgag aagtcaaagt ccgggggaat ttattcctgg caattttaat
                                                                        180
  tggactcctt atgtgagagc agcggctacc cagctggggt ggtggagcga acccgtcact
                                                                        240
  agtggacatg cagtggcaga gctcctggta accacctaga ggaatacaca ggcacatgtg
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 tgatgccaag cgtgacacct gtagcactca aatttgtctt gtttttgtct ttcggtgtgt
                                                                        360
                                                                        420
                                                                        431
       <210> 361
       <211> 351
       <212> DNA
       <213> Homo sapien
       <400> 361
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 actttcttct cagaagatag ggcacagcca ttgccttggc ctcacttgaa gggtctgcat
                                                                        60
 trgggtcctc tggtctcttg ccaagtttcc cagccactcg agggagaaat atcgggaggt
                                                                        120
ttgacttcct ccggggcttt cccgagggct tcaccgtgag ccctgcggcc ctcagggctg
                                                                       180
caatcctgga ttcaatgtct gaaacctcgc tctctgcctg ctggacttct gaggccgtca
                                                                       240
etgecactet gteeteeage tetgacaget ceteatetgt ggteetgttg t
                                                                       300
                                                                       351
       <210> 362
       <211> 463
       <212> DNA
      <213> Homo sapien
      <400> 362
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tgtagatgag ccggctgaag atcttgcgca tgcgcggctt cagggcgaag ttcttggcgc
                                                                        60
ecceggicae agaaatgace aggitgggig titteaggig ceagigetgg greageaget
                                                                      120
cgtaaaggat ttccgcgtcc gtgtcgcagg acagacgtat atacttccct ttcttcccca
                                                                      180
gtgtctcaaa ctgaatatcc ccaaaggcgt cggtaggaaa ttccttggtg tgtttcttgt
                                                                      240
agttccattt ctcactttgg ttgatctggg tgccttccat gtgctggctc tgggcatagc
                                                                      300
cacacttgca cacattctcc ctgataagca cgatggtgtg gacaggaagg aaggatttca
                                                                      360
ttgagcctgc ttatggaaac tggtattgtt agcttaaata gac
                                                                      420
                                                                      463
      <210> 363
      <211> 653
```

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<212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(653)
       <223> n = A, T, C \text{ or } G
       <400> 363
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                                                                        120
tgggaggcac tacgcaagat gggactgcgt cctggggtga gacatcctct ccttggagat
                                                                        180
ctaacgaaac ttctcaccta tgagttgtaa agcagaaata cctgnactac agacgagtgc
                                                                        240
ccaacagcaa ccccccggaa gtatgagttc ctctrgggcc tccgttccta ccatgagasc
                                                                        300
tagcaagatg naagtgttga gantcattgc agaggttcag aaaagagacc cntcgtgact
                                                                        360
ggtctgcaca gttcatggag gctgcagatg aggccttgga tgctctggat gctgctgcag
                                                                        420
ctgaggccga agcccgggct gaagcaagaa cccgcatggg aattggagat gaggctgtgt
                                                                        480
ntgggccctg gagctgggat gacattgagt ttgagctgct gacctgggat gaggaaggag
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attttggaga tccntggtcc agaattccat ttaccttctg ggccagatac caccagaatg
                                                                       600
cccgctccag attccctcag acctttgccg gtcccattat tggtcstggt ggt
                                                                        653
      <210> 364
      <211> 401
      <212> DNA
      <213> Homo sapien
      <400> 364
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acaaagccaa tgaatgactc taaaaacaat atttacattt aatggtttgt agacaataaa
                                                                       120
aaaacaaggt ggatagatct agaattgtaa cattttaaga aaaccatagc atttgacaga
                                                                       180
tgagaaagct caattataga tgcaaagtta taactaaact actatagtag taaagaaata
                                                                       240
cattleacae cetteatata aatteaetat ettggettga ggeaeteeat aaaatgtate
                                                                       300
acgtgcatag taaatcttta tatttgctat ggcgttgcac tagaggactt ggactgcaac
                                                                       360
aagtggatgc gcggaaaatg aaatcttctt caatagccca g
                                                                       401
      <210> 365
      <211> 356
      <212> DNA
      <213> Homo sapien
      <400> 365
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atgtttcagt gctagagcgt aggaatagac cctggcgtcc actgtgagat gttcttcagc
                                                                       120
taccagagca tcaagtetet geageaggte attettgggt aaagaaatga etteeacaaa
                                                                       180
ctctccatcc cctggctttg gcttcggcct tgcgttttcg gcatcatctc cgttaatggt
                                                                       240
gactgtcacg atgtgtatag tacagtttga caagcctggg tccatacaga ccgctggaga
                                                                       300
acatteggea atgreecett tgtagecagt trettetteg agetecegga gageag
                                                                       356
      <210> 366
      <211> 1851
      <212> DNA
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      <400> 366
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                                                                        60
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cttccgtgtt cttcattctt cttcaatagc cataaatctt ctagctctgg ctggctgttt
   teacticett taageettig tgactettee tetgatgica getttaagie tigttetgga
                                                                         120
   ttgctgtttt cagaagagat ttttaacatc tgtttttctt tgtagtcaga aagtaactgg
                                                                         180
  caaattacat gatgatgact agaaacagca tactctctgg ccgtctttcc agatcttgag
                                                                         240
  aagatacatc aacattttgc tcaagtagag ggctgactat acttgctgat ccacaacata
                                                                         300
  cagcaagtat gagagcagtt cttccatatc tatccagcgc atttaaattc gctttttct
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                                     75
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                                 90
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Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Xaa Tyr Asn Glu Asp
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Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val
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Leu 545	Ile	Val	Met	Leu	Arg 550	Asp	Thr	Asp	Val	Asn 555		Lys	Asp	Lys	Gln 560
Lys	Arg	Thr	Ala	Leu 565	His	Leu	Ala	Ser	Ala 570	Asn	Gly	Asn	Ser	Glu 575	Val
Val	Lys	Leu	Leu 580	Leu	Asp	Arg	Arg	Cys 585	Gln	Leu	Asn	Val	Leu 590	_	Asn
		595					600			Gln		605		_	
	610					615				Asp	620				_
Glu 625	Tyr	Gly	Asn	Thr	Thr 630	Leu	His	Tyr	Ala	Ile 635	Tyr	Asn	Glu	Asp	Lys 640
Leu	Met	Ala	Lys	Ala 645	Leu	Leu	Leu	Tyr	Gly 650	Ala	Asp	Ile	Glu	Ser 655	Lys
			660					665		Gly			670	Gln	_
Gln	Gln	Val 675	Val	Lys	Phe	Leu	Ile 680	Lys	Lys	Lys	Ala	Asn 685	Leu	Asn	Ala
Leu	Asp 690	Arg	Tyr	Gly	Arg	Thr 695	Ala	Leu	Ile	Leu	Ala 700	Val	Cys	Cys	Gly
Ser 705	Ala	Ser	Ile	Val	Ser 710	Leu	Leu	Leu	Glu	Gln 715	Asn	Ile	Asp	Val	Ser 720
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His	His	His	Val 740		Cys	Gln	Leu	Leu 745		Asp	Тух	Lys	Glu 750		Gln
Met	Leu	Lys 755	_	Ser	Ser	Glu	Asn 760		Asn	Pro	Glu	Gln 765		Leu	Lys
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Gly	Leu	Ile 835	Pro	Gln	Arg	Lys	Ser 840	Arg	Thr	Pro	Glu	Asn 845		Gln	Phe
Pro	Asp 850	Asn	Glu	Ser		Glu 855	Tyr	His	Arg	Ile	Cys 860		Leu	Val	Ser
Asp 865	Tyr	Lys	Glu	Lys	Gln 870	Met	Pro	Lys	Tyr	Ser 875	Ser	Glu	Asn	Ser	
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Glu	Glu	Met 915		Lys	His	Gly	Ser 920		His	Val	Gly	Phe 925	Pro	Glu	Asn
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Pro 945		Lys	Ser	Arg	Thr 950		Glu	Ser	Gln	Gln 955		Pro	Asp	Thr	Glu 960
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WO 00/04149 PCT/US99/15838 134

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Cys Glu Glu Gln Asn Thr Gly Ile Leu 980 985	
Glu Glu Lys Gln Ile Glu Val Val Glu	990
995 1000	
Leu Ser Cys Lys Lys Glu Lys Asp Ile	1005
	1000
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Gln Ser Gln Leu Pro Arg Thr His Met	Val Val Glu Val Asp Ser Met
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Pro Ala Ala Ser Ser Val Lys Lys Pro	Phe Gly Leu Arg Ser Lvs Met
Gly Lys Trp Cys Cys Arg Cys Phe Pro (	Cys Cys Arg Glu Ser Gly Lys
Ser Asn Val Gly Thr Ser Gly Asp His 7	Asp Asp Ser Ala Met Lys Thr
Leu Arg Ser Lys Met Gly Lys Trp Cys 1	Arg His Cys Phe Pro Cys Cys
Arg Gly Ser Gly Lys Ser Asn Val Gly A	1115
1123	1140
Ser Ala Met Lys Thr Leu Arg Asn Lys M	1135 Met Gly Lyg Tro Com Garage
±140 11/1C	
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Gly Asp Tyr Asp Asp Ser Ala Phe Met G	Hu Pro Arg Tyr His Val Arg
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Pro Arg Lys Asp Leu Ile Val Met Leu A	rg Asp Thr Asp Val Asn Lys 210 1215
Lys Asp Lys Gln Lys Arg Thr Ala Leu H	1215
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Gln Glu Asp Glu Cys Ala Leu Met Leu Le	eu Glu His Gly Thr Asp Pro
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Asn Ile Pro Asp Glu Tyr Gly Asn Thr Th	or Leu His Tyr Ala Ile Tyr
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1470	1305
His Glu Gln Lys Gln Gln Val Lys Ph	1325
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WO 00/04149 PCT/US99/15838

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Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val 70 75 Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn 85 90 Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser 105 Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe 120 Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu Asp Lys Leu His 135 Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met 150 155 Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln Lys Arg Thr Ala 165 170 Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu 180 185 Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr 200 205 Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met 215 220 Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn 230 235 Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys 245 250 Ala Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly 265 Leu Thr Pro Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val 280 Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr 295 300 Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile 310 315 Val Ser Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu 325 330 Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His Wal 345 Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile 360 Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu 375 380 Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser Gln Pro Glu Lys 390 395 Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Val Glu 405 410 Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly Leu Leu Glu Asn 425 Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asp Asn Gly Leu Ile Pro 440 Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe Pro Asp Asn Glu 455 Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser Asp Tyr Lys Glu 470 475 Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Glu Gly Ser Glu

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WO 00/04149 PCT/US99/15838 139

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tgtttgtggg gtgcagagat gggaggggtg gggcccaccc tggaagagtg gacagtgaca 1620
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gcatatccga cagttattct ctccaagtgg agacttacgg acagcatata attctccctg 2220
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 <210> 383
 <211> 155
 <212> PRT
 <213> Homo sapiens
 <400> 383
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Gly Lys Arg Gly Pro Leu Leu Gln Gly Leu Thr Trp Ala Thr Gly Gly
His Cys Phe Ser Ser Glu Glu Ser Gly Ala Val Asp Gly Ala Gly Gln
                             40
Lys Lys Asp Arg Ala Trp Leu Arg Cys Pro Glu Ala Val Ala Gly Phe
Pro Leu Gly Ser Asp Cys Arg Glu Gly Gly Arg Gln Gly Cys Gly Gly
Ser Asp Asp Glu Asp Asp Leu Gly Val Ala Pro Gly Leu Ala Pro Ala
                 85
Trp Ala Leu Thr Gln Pro Pro Ser Gln Ser Pro Gly Pro Gln Ser Leu
                                105
Pro Ser Thr Pro Ser Ser Ile Trp Pro Gln Trp Val Ile Leu Ile Thr
        115
                                                125
Glu Leu Thr Ile Pro Ser Pro Ala His Gly Pro Pro Trp Leu Pro Asn
                        135
Ala Leu Glu Arg Gly His Leu Val Arg Glu
145
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<211> 557
<212> DNA
<213> Homo sapiens
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ggggaagggt cccttttgca ttgccaagtg ccataaccat gagcactact ctaccatggt 180
tctgcctcct ggccaagcag gctggtttgc aagaatgaaa tgaatgattc tacagctagg 240
acttaacctt gaaatggaaa gtcttgcaat cccatttgca ggatccgtct gtgcacatgc 300
ctctgtagag agcagcattc ccagggacct tggaaacagt tggcactgta aggtgcttqc 360
tccccaagac acatcctaaa aggtgttgta atggtgaaaa cgtcttcctt ctttattgcc 420
ccttcttatt tatgtgaaca actgtttgtc tttttttgta tctttttaa actgtaaaqt 480
tcaattgtga aaatgaatat catgcaaata aattatgcga ttttttttt aaagtaaaaa 540
aaaaaaaaa aaaaaaa
                                                                   557
<210> 385
<211> 337
<212> DNA
<213> Homo sapiens
<400> 385
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gtttctctag cagcagatgg gttaggagga agtgacccaa gtggttgact cctatgtgca 120
teteaaagee atetgetgte ttegagtaeg gacacateat cacteetgea ttgttgatea 180
aaacgtggag gtgcttttcc tcagctaaga agcccttagc aaaagctcga atagacttag 240
tatcagacag gtccagtttc cgcaccaaca cctgctggtt ccctgtcgtg gtctggatct 300
ctttggccac caattccccc ttttccacat cccggca
                                                                  337
<210> 386
<211> 300
<212> DNA
<213> Homo sapiens
<400> 386
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gcccgctcgg cccagagggt gggcgcgggg ctgcctctac cggctggcgg ctgtaactca 120
gcgaccttgg cccgaagget ctagcaagga cccaccgacc ccagccgcgg cggcggcggc 180
gcggactttg cccggtgtgt ggggcggagc ggactgcgtg tccgcggacg ggcagcgaag 240
atgitageet tegetgeeag gacegiggae egateeeagg getgiggigt aaceteagee 300
<210> 387
<211> 537
<212> DNA
<213> Homo sapiens
<400> 387
gggccgagtc gggcaccaag ggactctttg caggcttcct tcctcggatc atcaaggctg 60
ecceptects typecateats at agence at atgasticg case agents the eagage 120
tgaaccagga ccggcttctg ggcggctgaa agggcaagg aggcaaggac cccgtctctc 180
ccacggatgg ggagaggca ggaggagacc cagccaagtg ccttttcctc agcactgagg 240
gagggggctt gtttcccttc cctcccggcg acaagctcca gggcagggct gtccctctqq 300
```

```
geggeeeage aetteeteag acaeaaette tteetgetge teeagtegtg gggateatea 360
 cttacccacc ccccaagttc aagaccaaat cttccagctg cccccttcgt gtttccctgt 420
 gtttgctgta gctgggcatg tctccaggaa ccaagaagcc ctcagcctgg tgtagtctcc 480
 ctgaccettg ttaatteett aagtetaaag atgatgaact teaaaaaaaa aaaaaaa
 <210> 388
 <211> 520
 <212> DNA
 <213> Homo sapiens
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 gtttgaagat tgcctcttct acagcttctg agaattgtgt tatttcactt gccaagtgaa 180
 ggacccctc cccaacatgc cccagcccac ccctaagcat ggtcccttgt caccaggcaa 240
 ccaggaaact gctacttgtg gacctcacca gagaccagga gggtttggtt agctcacagg 300
 acttccccca ccccagaaga ttagcatccc atactagact catactcaac tcaactaggc 360
 tcatactcaa ttgatggtta ttagacaatt ccatttcttt ctggttatta taaacagaaa 420
atctttcctc ttctcattac cagtaaaggc tcttggtatc tttctgttgg aatgatttct 480
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 <210> 389
 <211> 365
 <212> DNA
 <213> Homo sapiens
<400> 389
cgttgcccca gtttgacaga aggaaaggcg gagcttattc aaagtctaga gggagtggag 60
gagttaaggc tggatttcag atctgcctgg ttccagccgc agtgtgccct ctgctcccc 120
aacgactttc caaataatct caccagegee ttecagetca ggegteetag aagegtettg 180
aagcctatgg ccagetgtct ttgtgttccc tctcacccgc ctgtcctcac agctgagact 240
cccaggaaac cttcagacta ccttcctctg ccttcagcaa ggggcgttgc ccacattctc 300
tgagggtcag tggaagaacc tagactccca ttgctagagg tagaaagggg aagggtgctg 360
gggag
<210> 390
<211> 221
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(221)
<223> n = A, T, C \text{ or } G
<400> 390
tgcctctcca tcctggcccc gacttctctg tcaggaaagt ggggatggac cccatctgca 60
tacacggntt ctcatgggtg tggaacatet ctgcttgcgg tttcaggaag gcctctggct 120
getetangag tetganenga ntegttgeee cantntgaca naaggaaagg eggagettat 180
tcaaagtcta gagggagtgg aggagttaag gctggatttc a
                                                                   221
<210> 391
<211> 325
<212> DNA
<213> Homo sapiens
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<220>
<221> misc_feature
<222> (1)...(325)
<223> n = A, T, C \text{ or } G
<400> 391
tggagcaggt cccgaggcct ccctagagcc tgggggccgac tctgtgncga tgcangcttt 60
ctctcgcgcc cagcctggag ctgctcctgg catctaccaa caatcagncg aggcgagcag 120
tagccagggc actgctgcca acagccagtc cnnataccat catgtnaccc ggtgngctct 180
naantingat niccanagee clacecaten tagtietget eleccacegg niaccageee 240
cactgcccag gaatcctaca gccagtaccc tgtcccgacg tctctaccta ccagtacgat 300
gagaceteeg getactaeta tqace
<210> 392
<211> 277
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(277)
<223> n = A,T,C \text{ or } G
<400> 392
atattgttta actecttect ttatatettt taacatttte atggngaaag gttcacatet 60
agtotcactt nggcnagngn ctcctacttg agtotcttcc ccggcctgnn ccagtngnaa 120
antaccanga accgncatgn cttaanaacn ncctggtttn tgggttnntc aatgactgca 180
tqcagtgcac caccctgtcc actacgtgat gctgtaggat taaagtctca cagtgggcgg 240
ctgaggatac agcgccgcgt cctgtgttgc tggggaa
<210> 393
<211> 566
<212> DNA
<213> Homo sapiens
<400> 393
actagtccag tgtggtggaa ttcgcggccg cgtcgacgga caggtcagct gtctggctca 60
gtgatctaca ttctgaagtt gtctgaaaat gtcttcatga ttaaattcag cctaaacgtt 120
ttgccgggaa cactgcagag acaatgctgt gagtttccaa ccttagccca tctgcgggca 180
gagaaggtct agtttgtcca tcagcattat catgatatca ggactggtta cttggttaag 240
gaggggtcta ggagatctgt cccttttaga gacaccttac ttataatgaa gtatttggga 300
gggtggtttt caaaagtaga aatgtcctgt attccgatga tcatcctgta aacattttat 360
catttattaa tcatccctgc ctgtgtctat tattatattc atatctctac gctggaaact 420
cattetetge etgagtttta atttttgtee aaagttattt taatetatae aattaaaage 540
ttttgcctat caaaaaaaa aaaaaa
<210> 394
<211> 384
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
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<222> (1)...(384)
 <223> n = A, T, C \text{ or } G
 <400> 394
 gaacatacat gtcccggcac ctgagctgca gtctgacatc atcgccatca cgggcctcgc 60
 tgcaaattng gaccgggcca aggctggact gctggagcgt gtgaaggagc tacaggccna 120
 gcaggaggac cgggctttaa ggagttttaa gctgagtgtc actgtagacc ccaaatacca 180
 tcccaagatt atcgggagaa agggggcagt aattacccaa atccggttgg agcatgacgt 240
 gaacatccag tttcctgata aggacgatgg gaaccagccc caggaccaaa ttaccatcac 300
 agggtacgaa aagaacacag aagctgccag ggatgctata ctgagaattg tgggtgaact 360
 tgagcagatg gtttctgagg acgt
                                                                    384
 <210> 395
 <211> 399
 <212> DNA
 <213> Homo sapiens
 <400> 395
 ggcaaaactg tgtgacctca ataagacctc gcagatccaa ggtcaagtat cagaagtgac 60
 tetgacettg gaetecaaga ectacateaa eageetgget atattagatg atgagecagt 120
 tatcagaggt ttcatcattg cggaaattgt ggagtctaag gaaatcatgg cctctgaagt 180
attcacgtct ttccagtacc ctgagttctc tatagagttg cctaacacag gcagaattgg 240
ccagctactt gtctgcaatt gtatcttcaa gaataccctg gccatccctt tgactgacgt 300
caagttetet ttggaaagee tgggeatete eteactacag acetetgace atgggaeggt 360
gcagcctggt gagaccatcc aatcccaaat aaaatgcac
<210> 396
<211> 403
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(403)
<223> n = A,T,C or G
<400> 396
tggagttntc agtgcaaaca agccataaag.cttcagtagc aaattactgt ctcacagaaa 60
gacattttca acttctgctc cagctgctga taaaacaaat catgtgttta gcttgactcc 120
agacaaggac aacctgttcc ttcataactc tctagagaaa aaaaggagtt gttagtagat 180
actaaaaaaa gtggatgaat aatctggata tttttcctaa aaagattcct tgaaacacat 240
taggaaaatg gagggcctta tgatcagaat gctagaatta gtccattgtg ctgaagcagg 300
gtttagggga gggagtgagg gataaaagaa ggaaaaaaag aagagtgaga aaacctattt 360
atcaaagcag gtgctatcac tcaatgttag gccctgctct ttt
                                                                   403
<210> 397
<211> 100
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(100)
<223> n = A,T,C or G
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<400> 397
actagincag igiggiggaa ticgcggccg cgicgaccta naanccatci ciatagcaaa 60
tccatccccg ctcctggttg gtnacagaat gactgacaaa
<210> 398
<211> 278
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(278)
<223> n = A,T,C or G
<400> 398
gcggccgcgt cgacagcagt tccgccagcg ctcgcccctg ggtggggatg tgctgcacgc 60
ccacctggac atctggaagt cagcggcctg gatgaaagag cggacttcac ctggggcgat 120
tcactactgt gcctcgacca gtgaggagag ctggaccgac agcgaggtgg actcatcatg 180
ctccgggcag cccatccacc tgtggcagtt cctcaaggag ttgctactca agccccacag 240
ctatggccgc ttcattangt ggctcaacaa ggagaagg
                                                                278
<210> 399
<211> 298
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(298)
<223> n = A,T,C or G
<400> 399
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ggggtgccng catggagcgc atgggcgcgg gcctgggcca cggcatggat cgcgtgggct 120
ccgagatcga gcgcatgggc ctggtcatgg accgcatggg ctccgtggag cgcatgggct 180
ccggcattga gcgcatgggc ccgctgggcc tcgaccacat ggcctccanc attgancgca 240
tgggccagac catggagcgc attggctctg gcgtggagcn catgggtgcc ggcatggg
<210> 400
<211> 548
<212> DNA
<213> Homo sapiens
<400> 400
acatcaacta cttcctcatt ttaaggtatg gcagttccct tcatcccctt ttcctgcctt 60
gtacatgtac atgtatgaaa tttccttctc ttaccgaact ctctccacac atcacaaggt 120
tgagtctctt ttttccacgt ttaaggggcc atggcaggac ttagagttgc gagttaagac 240
tgcagagggc tagagaatta tttcatacag gctttgaggc cacccatgtc acttatcccg 300
tataccetet caccatecce ttgtctacte tgatgecece aagatgeaac tgggcageta 360
gttggcccca taattctggg cctttgttgt ttgttttaat tacttgggca tcccaggaag 420
ctttccagtg atctcctacc atgggccccc ctcctgggat caagcccctc ccaggccctg 480
tecceageee etectgeeee ageceaeeeg ettgeettgg tgeteageee teccattggg 540
agcaggtt
                                                                548
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<210> 401

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<211> 355
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <222> (1)...(355)
 <223> n = A,T,C or G
 <400> 401
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 tgatgtctcc aagtagtcca ccttcattta actctttgaa actgtatcat ctttgccaag 120
 taagagtggt ggcctatttc agctgctttg acaaaatgac tggctcctga cttaacgttc 180
 tataaatgaa tgtgctgaag caaagtgccc atggtggcgg cgaagaagan aaagatgtgt 240
 tttgttttgg actetetgtg gtecetteca atgetgnggg tttecaacca ggggaagggt 300
 cccttttgca ttgccaagtg ccataaccat gagcactact ctaccatggn tctgc
 <210> 402
 <211> 407
 <212> DNA
 <213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(407)
<223> n = A,T,C or G
<400> 402
atggggcaag ctggataaag aaccaagacc cactggagta tgctgtcttc aagaaaccca 60
teteacatge ggtggcatae ataggeteaa aataaaggaa tggagaaaaa tattteaage 120
aaatggaaaa cagaaaaaag caggtgttgc actcctactt tctgacaaaa cagactatgc 180
gaataaagat aaaaaagaga aggacattac aaaggtggtc ctgacctttg ataaatctca 240
ttgcttgata ccaacctggg ctgttttaat tgcccaaacc aaaaggataa tttgctgagg 300
ttgtggagct tctcccctgc agagagtccc tgatctccca aaatttggtt gagatgtaag 360
gntgattttg ctgacaactc cttttctgaa gttttactca tttccaa
<210> 403
<211> 303
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(303)
<223> n = A,T,C or G
<400> 403
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tcctaagcaa gagccatggc atggtgaaaa tgcaaaagga gagtctggcc aatctacaaa 120
tagagaacaa gacctactca gtcatgaaca aaaaggcaga caccaacatg gatctcatgg 180
gggattggat attgtaatta tagagcagga agatgacagt gatcgtcatt tggcacaaca 240
tottaacaac gaccgaaace cattatttac ataaacetec atteggtaac catgttgaaa 300
gga
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WO 00/04149 PCT/US99/15838 147

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<210> 404
<211> 225
<212> DNA
<213> Homo sapiens
<400> 404
aagtgtaact tttaaaaaatt tagtggattt tgaaaaattct tagaggaaaag taaaggaaaa 60
attgttaatg cactcattta cctttacatg gtgaaagttc tctcttgatc ctacaaacag 120
acattttcca ctcgtgtttc catagttgtt aagtgtatca gatgtgttgg gcatgtgaat 180
ctccaagtgc ctgtgtaata aataaagtat ctttatttca ttcat
<210> 405
<211> 334
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(334)
<223> n = A, T, C or G
<400> 405
gagctgttat actgtgagtt ctactaggaa atcatcaaat ctgagggttg tctggaggac 60
ttcaatacac ctcccccat agtgaatcag cttccagggg gtccagtccc tctccttact 120
tcatccccat cccatgccaa aggaagaccc tccctccttg gctcacagcc ttctctaggc 180
ttcccagtgc ctccaggaca gagtgggtta tgttttcagc tccatccttg ctgtgagtgt 240
ctggtgcggt tgtgcctcca gcttctgctc agtgcttcat ggacagtgtc cagcccatgt 300
cactetecae teteteanng tggateceae eeet
<210> 406
<211> 216
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (216)
<223> n = A,T,C or G
<400> 406
tttcatacct aatgagggag ttganatnac atnnaaccag gaaatgcatg gatctcaang 60
gaaacaaaca cccaataaac tcggagtggc agactgacaa ctgtgagaca tgcacttgct 120
acnaaacaca aatttnatgt tgcacccttg tttctacacc tgtgggttat qacaaagaca 180
actgccaaag aatnttcaag aaggaggact gccant
<210> 407
<211> 413
<212> DNA
<213> Homo sapiens
<400> 407
gctgacttgc tagtatcatc tgcattcatt gaagcacaag aacttcatgc cttgactcat 60
gtaaatgcaa taggattaaa aaataaattt gatatcacat ggaaacagac aaaaaatatt 120
gtacaacatt gcacccagtg tcagattcta cacctggcca ctcaggaagc aagagttaat 180
cccagaggtc tatgtcctaa tgtgttatgg caaatggatg tcatgcacgt accttcattt 240
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ggaaaattgt catttgtcca tgtgacagtt gatacttatt cacatttcat atgggcaacc 300
  tgccagacag gagaaagtct tcccatgtta aaagacattt attatcttgt tttcctgtca 360
  tgggagttcc agaaaaagtt aaaacagaca atgggccagg ttctgtagta aag
  <210> 408
  <211> 183
  <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <222> (1)...(183)
 <223> n = A, T, C or G
 <400> 408
 ggagctngcc ctcaattcct ccatntctat gttancatat ttaatgtctt ttgnnattaa 60
 tnettaacta gttaateett aaagggetan ntaateetta actagteeet ceattgtgag 120
 cattatectt ceagtatten cettetnttt tatttactee tteetggeta eccatgtact 180
 ntt
 <210> 409
 <211> 250
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <222> (1)...(250)
 <223> n = A, T, C \text{ or } G
<400> 409
cccacgcatg ataagctett tatttetgta agteetgeta ggaaateate aaatetgaeg 60
gtggtttggg ggacctgaac aaacctcctg taattaatca gctttcagtt tctccccta 120
gtccctcctt caacaacata ggaggatcct ccccttcttt ctgctcacgg ccttatctag 180
gcttcccagt gcccccagga cagcgtgggc tatgtttaca gcgcntcctt gctggggggg 240
ggccntatgc
                                                                    250
<210> 410
<211> 306
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(306)
<223> n = A,T,C or G
<400> 410
ggctggtttg caagaatgaa atgaatgatt ctacagctag gacttaacct tgaaatggaa 60
agtettgeaa teccatttge aggateegte tgtgeacatg cetetgtaga gageageatt 120
cccagggacc ttggaaacag ttggcactgt aaggtgcttg ctccccaaga cacatcctaa 180
aaggtgttgt aatggtgaaa accgcttcct tctttattgc cccttcttat ttatgtgaac 240
nactggttgg ctttttttgn atcttttta aactggaaag ttcaattgng aaaatgaata 300
                                                                   306
```

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<210> 411
<211> 261
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(261)
<223> n = A, T, C or G
<400> 411
agagatattn cttaggtnaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatcttttg tatttaagga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttacccat cagttccagc 240
cttctctcaa ggngaggcaa a
<210> 412
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
<400> 412
gttcaatgtt acctgacatt tctacaacac cccactcacc gatgtattcg ttgcccagtg 60
ggaacatacc agcctgaatt tggaaaaaat aattgtgttt cttgcccagg aaatactacg 120
actgactttg atggctccac aaacataacc cagtgtaaaa acagaagatg tggagggag 180
ctgggagatt tcactgggta cattgaattc ccaaactacc cangcaatta cccagccaac 240
                                                                    241
<210> 413
<211> 231
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (231)
<223> n = A,T,C \text{ or } G
<400> 413
aactettaca atecaagtga eteatetgtg tgettgaate etttecaetg teteatetee 60
ctcatccaag tttctagtac cttctctttg ttgtgaagga taatcaaact gaacaacaaa 120
aagtttactc tcctcatttg gaacctaaaa actctcttct tcctgggtct gagggctcca 180
agaatccttg aatcanttct cagatcattg gggacaccan atcaggaacc t
<210> 414
<211> 234
<212> DNA
<213> Homo sapiens
```

```
<400> 414
 actgtccatg aagcactgag cagaagctgg aggcacaacg caccagacac tcacagcaag 60
 gatggagctg aaaacataac ccactctgtc ctggaggcac tgggaagcct agagaaggct 120
 gtgagccaag gagggagggt cttcctttgg catgggatgg ggatgaagta aggagaggga 180
 ctggaccccc tggaagctga ttcactatgg ggggaggtgt attgaagtcc tcca
 <210> 415
 <211> 217
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <222> (1)...(217)
 <223> n = A,T,C or G
 <400> 415
 gcataggatt aagactgagt atcttttcta cattctttta actttctaag gggcacttct 60
 caaaacacag accaggtage aaatetecae tgetetaagg nteteaceae caetttetea 120
 cacctagcaa tagtagaatt cagtcctact tctgaggcca gaagaatggt tcagaaaaat 180
 antggattat aaaaaataac aattaagaaa aataatc
                                                                    217
 <210> 416
 <211> 213
 <212> DNA
 <213> Homo sapiens
 <220>
<221> misc_feature
<222> (1)...(213)
<223> n = A,T,C or G
<400> 416
atgcatatnt aaagganact gcctcgcttt tagaagacat ctggnctgct ctctgcatga 60
ggcacagcag taaagctctt tgattcccag aatcaagaac tctccccttc agactattac 120
cgaatgcaag gtggttaatt gaaggccact aattgatgct caaatagaag gatattgact 180
atattggaac agatggagtc tctactacaa aaq
                                                                   213
<210> 417
<211> 303
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(303)
<223> n = A,T,C or G
<400> 417
nagtetteag geceateagg gaagtteaca etggagagaa gteatacata tgtaetgtat 60
gtgggaaagg ctttactctg agttcaaatc ttcaagccca tcagagagtc cacactggag 120
agaagccata caaatgcaat gagtgtggga agagcttcag gagggattcc cattatcaag 180
ttcatctagt ggtccacaca ggagagaaac cctataaatg tgagatatgt gggaagggct 240
tcantcaaag ttcgtatctt caaatccatc ngaaggncca cagtatanan aaacctttta 300
agt
                                                                  303
```

```
<210> 418
<211> 328
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(328)
<223> n = A,T,C or G
<400> 418
tttttggcgg tggtggggca gggacgggac angagtetea etetgttgee caggetggag 60
tgcacaggca tgatctcggc tcactacaac ccctgcctcc catgtccaag cgattcttqt 120
gcctcagcct tccctgtagc tagaattaca ggcacatgcc accacaccca gctagtttt 180
gtatttttag tagagacagg gtttcaccat gttggccagg ctggtctcaa actcctnacc 240
tcagnggtca ggctggtctc aaactcctga cctcaagtga tctgcccacc tcagcctccc 300
aaagtgctan gattacaggc cgtgagcc
                                                                   328
<210> 419
<211> 389
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(389)
<223> n = A,T,C or G
<400> 419
cctcctcaag acggcctgtg gtccgcctcc cggcaaccaa gaagcctgca gtgccatatg 60
acccctgagc catggactgg agcctgaaag gcagcgtaca ccctgctcct. gatcttgctq 120
cttgtttcct ctctgtggct ccattcatag cacagttgtt gcactgaggc ttqtqcaggc 180
cgagcaaggc caagctggct caaagagcaa ccagtcaact ctgccacggt gtgccaggca 240
ceggttetee agecaceaac eteacteget ecegeaaatg geacateagt tettetacee 300
taaaaggtagg accaaagggc atctgctttt ctgaagtcct ctgctctatc aqccatcacq 360
tggcagccac tcnggctgtg tcgacgcqq
                                                                   389
<210> 420
<211> 408
<212> DNA
<213> Homo sapiens
<400> 420
gttcctccta actcctgcca gaaacagctc tcctcaacat gagaqctqca cccttcctcc 60
tggccagggc agcaagcett agcettgget tettgtttet getttttte tggctagace 120
gaagtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attcttgaat gagtcctata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg aagtgctatg acaaacctgg caagcccg
<210> 421
<211> 352
<212> DNA.
```

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<213> Homo sapiens
  <220>
 <221> misc_feature
 <222> (1) ... (352)
 <223> n = A, T, C \text{ or } G
 <400> 421
 gctcaaaaat ctttttactg atnggcatgg ctacacaatc attgactatt acggaggcca 60
 gaggagaatg aggcctggcc tgggagccct gtgcctacta naagcacatt agattatcca 120
 ttcactgaca gaacaggtct tttttgggtc cttcttctcc accacnatat acttgcagtc 180
 ctccttcttg aagattcttt ggcagttgtc tttgtcataa cccacaggtg tagaaacaag 240
 ggtgcaacat gaaatttctg tttcgtagca agtgcatgtc tcacaagttg gcangtctgc 300
 cactccgagt ttattgggtg tttgtttcct ttgagatcca tgcatttcct gg
 <210> 422
 <211> 337
 <212> DNA
 <213> Homo sapiens
 <400> 422
atgccaccat gctggcaatg cagcgggcgg tcgaaggcct gcatatccag cccaagctgg 60
cgatgatcga cggcaaccgt tgcccgaagt tgccgatgcc agccgaagcg gtggtcaagg 120
gcgatagcaa ggtgccggcg atcgcggcgg cgtcaatcct ggccaaggtc agccgtgatc 180
gtgaaatggc agctgtcgaa ttgatctacc cgggttatgg catcggcggg cataagggct 240
atccgacacc ggtgcacctg gaagccttgc agcggctggg gccgacgccg attcaccgac 300
gcttcttccg ccggtacggc tggcctatga aaattat
<210> 423
<211> 310
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(310)
<223> n = A,T,C or G
<400> 423
gctcaaaaat ctttttactg atatggcatg gctacacaat cattgactat tagaggccag 60
aggagaatga ggcctggcct gggagccctg tgcctactan aagcncatta gattatccat 120
tcactgacag aacaggtctt ttttgggtcc ttcttctcca ccacgatata cttgcagtcc 180
tccttcttga agattctttg gcagttgtct ttgtcataac ccacaggtgt anaaacaagg 240
gtgcaacatg aaatttctgt ttcgtagcaa gtgcatgtct cacagttgtc aagtctgccc 300
tccgagttta
<210> 424
<211> 370
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(370)
<223> n = A,T,C or G
```

```
<400> 424
qctcaaaaat ctttttactg ataggcatgg ctacacaatc attgactatt agaggccaga 60
ggagaatgag gcctggcctg ggagccctgt gcctactaga agcacattag attatccatt 120
cactgacaga acaggtettt tttgggteet tettetecae cacgatatae ttgcagteet 180
ccttcttgaa gattctttgg cagttgtctt tgtcataacc cacaggtgta gaaacatcct 240
gqttgaatct cctggaactc cctcattagg tatgaaatag catgatgcat tgcataaagt 300
cacgaaggtg gcaaagatca caacgctgcc cagganaaca ttcattgtga taagcaggac 360
tccgtcgacg
<210> 425
<211> 216
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(216)
<223> n = A, T, C \text{ or } G
<400> 425
taacaacnca acatcaaggn aaananaaca ggaatggntg actntgcata aatnggccga 120
anattateca ttatnttaag ggttgaette aggntaeage acacagaeaa acatgeecag 180
gaggntntca ggaccgctcg atgtnttntg aggagg
                                                                216
<210> 426
<211> 596
<212> DNA
<213> Homo sapiens
<400> 426
cttccagtga ggataaccct gttgccccgg gccgaggttc tccattaggc tctgattgat 60
tggcagtcag tgatggaagg gtgttctgat cattccgact gccccaaggg tcgctggcca 120
gctctctgtt ttgctgagtt ggcagtagga cctaatttgt taattaagag tagatggtga 180
gctgtccttg tattttgatt aacctaatgg ccttcccagc acgactcgga ttcagctgga 240
gacatcacgg caacttttaa tgaaatgatt tgaagggcca ttaagaggca cttcccgtta 300
ttaggcagtt catctgcact gataacttct tggcagctga gctggtcgga gctgtggccc 360
aaacgcacac ttggcttttg gttttgagat acaactctta atcttttagt catgcttgag 420
ggtggatggc cttttcagct ttaacccaat ttgcactgcc ttggaagtgt agccaggaga 480
atacactcat atactcgtgg gcttagaggc cacagcagat gtcattggtc tactgcctga 540
gtcccgctgg tcccatccca ggaccttcca tcggcgagta cctgggagcc cgtgct
<210> 427
<211> 107
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(107)
<223> n = A,T,C or G
<400> 427
gaagaattca agttaggttt attcaaaggg cttacngaga atcctanacc caggncccag 60
```

WO 00/04149 PCT/US99/15838 154

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cccgggagca gccttanaga gctcctgttt gactgcccgg ctcagng
                                                                    107
 <210> 428
 <211> 38
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <222> (1)...(38)
 <223> n = A,T,C or G
 <400> 428
 gaacttccna anaangactt tattcactat tttacatt
                                                                    38
 <210> 429
 <211> 544
 <212> DNA
 <213> Homo sapiens
 <400> 429
 ctttgctgga cggaataaaa gtggacgcaa gcatgacctc ctgatgaggg cgctgcattt 60
attgaagage ggetgeagee etgeggttea gattaaaate egagaattgt atagaegeeg 120
atatccacga actcttgaag gactttctga tttatccaca atcaaatcat cggttttcag 180
tttggatggt ggctcatcac ctgtagaacc tgacttggcc gtggctggaa tccactcgtt 240
geettecact teagttacae eteacteace atcetetet gttggttetg tgetgettea 300
agatactaag cccacatttg agatgcagca gccatctccc ccaattcctc ctgtccatcc 360
tgatgtgcag ttaaaaaatc tgccctttta tgatgtcctt gatgttctca tcaagcccac 420
gagtttagtt caaagcagta ttcagcgatt tcaagagaag ttttttattt ttgctttgac 480
acctcaacaa gttagagaga tatgcatatc cagggatttt ttgccaggtg gtaggagaga 540
ttat
<210> 430
<211> 507
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (507)
<223> n = A,T,C or G
<400> 430
cttatcncaa tggggctccc aaacttggct gtgcagtgga aactccgggg gaattttgaa 60
gaacactgac acccatcttc caccccgaca ctctgattta attgggctgc agtgagaaca 120
gagcatcaat ttaaaaagct gcccagaatg ttntcctggg cagcgttgtg atctttgccn 180
ccttcgtgac tttatgcaat gcatcatgct atttcatacc taatgaggga gttccaggag 240
attcaaccag gatgtttcta cncctgtggg ttatgacaaa gacaactgcc aaagaatntt 300
caagaaggag gactgcaagt atatcgtggt ggagaagaag gacccaaaaa agacctgttc 360
tgtcagtgaa tggataatct aatgtgcttc tagtaggcac agggctccca ggccaggcct 420
catteteete tggeetetaa tagteaatga ttgtgtagee atgeetatea gtaaaaagat 480
ttttgagcaa aaaaaaaaa aaaaaaa
                                                                  507
<210> 431
<211> 392
```

```
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(392)
<223> n = A, T, C or G
<400> 431
gaaaattcag aatggataaa aacaaatgaa gtacaaaata tttcagattt acatagcgat 60
aaacaagaaa gcacttatca ggaggactta caaatggaag tacactctan aaccatcatc 120
tatcatggct aaatgtgaga ttagcacagc tgtattattt gtacattgca aacacctaga 180
aagagatggg aaacaaaatc ccaggagttt tgtgtgtgga gtcctgggtt ttccaacaga 240
catcattcca gcattctgag attagggnga ttggggatca ttctggagtt ggaatgttca 300
acaaaagtga tgttgttagg taaaatgtac aacttctgga tctatgcaga cattgaaggt 360
gcaatgagtc tggcttttac tctgctgttt ct
<210> 432
<211> 387
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(387)
<223> n = A, T, C or G
<400> 432
ggtatccnta cataatcaaa tatagctgta gtacatgttt tcattggngt agattaccac 60
aaatgcaagg caacatgtgt agatctcttg tcttattctt ttgtctataa tactgtattg 120
ngtagtccaa geteteggna gtecagecae tgngaaacat getecettta gattaacete 180
gtggacnctn ttgttgnatt gtctgaactg tagngccctg tattttgctt ctgtctgnga 240
attctgttgc ttctggggca tttccttgng atgcagagga ccaccacaca gatgacagca 300
atctgaattg ntccaatcac agctgcgatt aagacatact gaaatcgtac aggaccggga 360
acaacgtata gaacactgga gtccttt
<210> 433
<211> 281
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(281)
<223> n = A,T,C or G
<400> 433
ttcaactagc anagaanact gcttcagggn gtgtaaaatg aaaggcttcc acgcagttat 60
ctgattaaag aacactaaga gagggacaag gctagaagcc gcaggatgtc tacactatag 120
caggenetat ttgggttgge tggaggget gtggaaaaca tggagagatt ggegetggag 180
atcgccgtgg ctattcctcn ttgntattac accagngagg ntctctgtnt gcccactggt 240
tnnaaaaccg ntatacaata atgatagaat aggacacaca t
                                                                   281
<210> 434
<211> 484
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<212> DNA
 <213> Homo sapiens
 <400> 434
 ttttaaaata agcatttagt gctcagtccc tactgagtac tctttctctc ccctcctctg 60
 aatttaattc tttcaacttg caatttgcaa ggattacaca tttcactgtg atgtatattg 120
 tgttgcaaaa aaaaaaaagt gtctttgttt aaaattactt ggtttgtgaa tccatcttgc 180
 tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa acatctgaag 240
 agctagtcta tcagcatctg acaggtgaat tggatggttc tcagaaccat ttcacccaga 300
 cagectgttt ctatectgtt taataaatta gtttgggtte tetacatgca taacaaacce 360
 tgctccaatc tgtcacataa aagtctgtga cttgaagttt agtcagcacc cccaccaaac 420
 tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataaag tacccatgtc 480
 ttta
                                                                    484
 <210> 435
 <211> 424
 <212> DNA
 <213> Homo sapiens
 <400> 435
gegeegetea gageaggtea etttetgeet teeaegteet eetteaagga ageeeeatgt 60
gggtagettt caatategea ggttettaet eetetgeete tataagetea aacceaceaa 120
cgatcgggca agtaaacccc ctccctcgcc gacttcggaa ctggcgagag ttcagcgcag 180
atgggcctgt ggggagggg caagatagat gaggggagc ggcatggtgc ggggtgaccc 240
cttggagaga ggaaaaaggc cacaagaggg gctgccaccg ccactaacgg agatggccct 300
ggtagagacc tttgggggtc tggaacctct ggactcccca tgctctaact cccacactct 360
gctatcagaa acttaaactt gaggattttc tctgtttttc actcgcaata aartcagagc 420
aaac
<210> 436
<211> 667
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(667)
<223> n = A,T,C or G
<400> 436
accttgggaa nactctcaca atataaaggg tcgtagactt tactccaaat tccaaaaagg 60
tcctggccat gtaatcctga aagttttccc aaggtagcta taaaatcctt ataagggtgc 120
agcetettet ggaatteete tgattteaaa gteteaetet caagttettg aaaacgaggg 180
cagttcctga aaggcaggta tagcaactga tcttcagaaa gaggaactgt gtgcaccggg 240
atgggctgcc agagtaggat aggattccag atgctgacac cttctggggg aaacagggct 300
gccaggtttg tcatagcact catcaaagtc cggtcaacgt ctgtgcttcg aatataaacc 360
tgttcatgtt tataggactc attcaagaat tttctatatc tctttcttat atactctcca 420
agttcataat gctgctccat gcccagctgg gtgagttggc caaatccttg tggccatgag 480
gattccttta tggggtcagt gggaaaggtg tcaatgggac ttcggtctcc atgccgaaac 540
accaaagtca caaacttcaa ctccttggct agtacacttc ggtctagcca gaaaaaaagc 600
agaaacaaga agccaaggct aaggcttgct gccctgccag gaggaggggt gcagctctca 660
tgttgag
                                                                  667
<210> 437
<211> 693
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WO 00/04149 PCT/US99/15838 ··· 157

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<212> DNA
<213> Homo sapiens
<400> 437
ctacgtctca accctcattt ttaggtaagg aatcttaagt ccaaagatat taagtgactc 60
acacagccag gtaaggaaag ctggattggc acactaggac tctaccatac cgggttttgt 120
taaagctcag gttaggaggc tgataagctt ggaaggaact tcagacagct ttttcagatc 180
ataaaagata attottagco catgttotto tocagagcag acotgaaatg acagcacago 240
aggtactcct ctattttcac ccctcttgct tctactctct ggcagtcaga cctgtgggag 300
gccatgggag aaagcagctc tctggatgtt tgtacagatc atggactatt ctctgtggac 360
cattlctcca ggttacccta ggtgtcacta ttggggggac agccagcatc tttagctttc 420
atttgagttt ctgtctgtct tcagtagagg aaacttttgc tcttcacact tcacatctga 480
acacctaact gctgttgctc ctgaggtggt gaaagacaga tatagagctt acaqtattta 540
tcctatttct aggcactgag ggctgtgggg taccttgtgg tgccaaaaca gatcctqttt 600
taaggacatg ttgcttcaga gatgtctgta actatctggg ggctctgttg gctctttacc 660
ctgcatcatg tgctctcttg gctgaaaatg acc
                                                                   693
<210> 438
<211> 360
<212> DNA
<213> Homo sapiens
<400> 438
ctgcttatca caatgaatgt tctcctgggc agcgttgtga tctttgccac cttcgtgact 60
ttatgcaatg catcatgcta tttcatacct matgagggag ttccaggaga ttcaaccagg 120
atgtttctac acctgtgggt tatgacaaag acaactgcca aagaatcttc aagaaggagg 180
actgcaagta tatctggtgg agaagaagga cccaaaaaaag acctgttctg tcagtgaatg 240
gataatctaa tgtgcttcta gtaggcacag ggctcccagg ccaggcctca ttctcctctg 300
gcctctaata gtcaataatt gtgtagccat gcctatcagt aaaaagattt ttgagcaaac 360
<210> 439
<211> 431
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(431)
<223> n = A,T,C or G
<400> 439
gttcctnnta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcett agcettgget tettgtttet getttttte tggctagace 120
gaagtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaqa 300
gatatagaaa attcttgaat gagtcctata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
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<212> DNA
<213> Homo sapiens
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  tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
  aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttacccat cagttccagc 240
  cttctctcaa ggagaggcaa agaaaggaga tacagtggag acatctggaa agttttctcc 300
  actggaaaac tgctactatc tgtttttata tttctgttaa aatatatgag gctacagaac 360
 taaaaattaa aacctctttg tgtcccttgg tcctggaaca tttatgttcc ttttaaagaa 420
 acaaaaatca aactttacag aaagatttga tgtatgtaat acatatagca gctcttgaag 480
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 <212> DNA
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 gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
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 aatttaqtaq
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 <211> 362
 <212> DNA
 <213> Homo sapiens
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cttcacttct gatacttgta aattaatctt ttattgcact tgttttgacc attaagctat 180
atgtttagaa atggtcattt tacggaaaaa ttagaaaaat tctgataata gtgcagaata 240
aatgaattaa tgttttactt aatttatatt gaactgtcaa tgacaaataa aaattctttt 300
tgattatttt ttgttttcat ttaccagaat aaaaactaag aattaaaagt ttgattacag 360
tc
<210> 443
<211> 624
<212> DNA
<213> Homo sapiens
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<222> (1)...(624)
<223> n = A, T, C or G
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ttgaaagaat taaattcaga ggaggggaga gaaagagtac tcagtaggga ctgagcacta 120
aatgcttatt ttaaaagaaa tgtaaagagc agaaagcaat tcaggctacc ctgccttttg 180
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WO 00/04149 PCT/US99/15838 159

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cccaaaccac agaaaatggg gtgaaattgg ccaactttct attaacttgg cttcctgttt 300
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taacgcctac aaaacactta aacatagata acataggtgc aagtactatg tatctqqtac 420
atggtaaaca toottattat taaagtoaac gotaaaatga atgtgtgtgc atatgctaat 480
agtacagaga gagggcactt aaaccaacta agggcctgga gggaaggttt cctggaaaga 540
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<210> 444
<211> 425
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(425)
<223> n = A,T,C or G
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gaagettigt ccaggeeigt gigtgaacce aatgittige tiagaaatag aacaagtaag 120
ttcattgcta tagcataaca caaaatttgc ataagtggtg gtcagcaaat ccttgaatgc 180
tgcttaatgt gagaggttgg taaaatcctt tgtgcaacac tctaactccc tgaatgtttt 240
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cetetgeaat etgecacete etgetggeag gatttgtttt tgeateetgt qaaqaqceaa 360
ggaggcacca gggcataagt gagtagactt atggtcgacg cggccgcgaa tttagtagta 420
gtaga
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<211> 414
<212> DNA
<213> Homo sapiens
<220>
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<222> (1)...(414)
<223> n = A,T,C or G
<400> 445
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tgaaattctt tgcatgtggc agattattgg atgtagtttc ctttaactag catataaatc 180
tggtgtgttt cagataaatg aacagcaaaa tgtggtggaa ttaccatttg gaacattgtg 240
aatgaaaaat tgtgtctcta gattatgtaa caaataacta tttcctaacc attgatcttt 300
ggatttttat aatcctactc acaaatgact aggcttctcc tcttgtattt tgaagcagtg 360
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<211> 631
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<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(631)
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  atgctggtta tactggacaa cactgtgaaa aaaaggacta cagtgttcta tacgttgttc 180
  ccggtcctgt acgatttcag tatgtcttaa tcgcagctgt gattggaaca attcagattg 240
  ctgtcatctg tgtggtggtc ctctgcatca caagggccaa actttaggta atagcattgg 300
  actgagattt gtaaactttc caaccttcca ggaaatgccc cagaagcaac agaattcaca 360
  gacagaagca aaatacaggg cactacagtt cagacaatac aacaagagcg tccacgaggt 420
  taatctaaag ggagcatgtt tcacagtggc tggactaccg agagcttgga ctacacaata 480
  cagtattata gacaaaagaa taagacaaga gatctacaca tgttgccttg catttgtggt 540
  aatctacacc aatgaaaaca tgtactacag ctatatttga ttatgtatgg atatatttga 600
  aatagtatac attgtcttga tgttttttct g
  <210> 447
  <211> 585
  <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc feature
 <222> (1)...(585)
 <223> n = A, T, C \text{ or } G
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 gcctcttctg gaattcctct gatttcaaag tctcactctc aagttcttga aaacgagggc 180
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 ccaggtttgt catagcactc atcaaagtcc ggtcaacgtc tgtgcttcga atataaacct 360
 gttcatgttt ataggactca ttcaagaatt ttctatatct ctttcttata tactctccaa 420
 gttcataatg ctgctccatg cccagctggg tgagttggcc aaatccttgt ggccatgagg 480
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 <210> 448
 <211> 93
 <212> DNA
 <213> Homo sapiens
<220>
<221> misc_feature
 <222> (1)...(93)
<223> n = A,T,C or G
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ggctccctag tgccctggag agganggggc tag
                                                                   93
<210> 449
<211> 706
<212> DNA
<213> Homo sapiens
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WO 00/04149 PCT/US99/15838 161

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<220>
<221> misc feature
<222> (1)...(706)
<223> n = A, T, C \text{ or } G
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cctggagagg aggtgtctag tcagagagta gtcctggaag gtggcctctg ngaggagcca 180
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cgacggccag tgaattgaat ttaggtgacn ctatagaaga gctatgacgt cgcatgcacg 420
cgtacgtaag cttggatcct ctagagcggc cgcctactac tactaaattc gcggccgcgt 480
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aacaggttga acctgggagg tggaggttgc aatgagctga gatcaggccn ctgcncccca 660
gcatggatga cagagtgaaa ctccatctta aaaaaaaaa aaaaaa
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<211> 493
<212> DNA
<213> Homo sapiens
<400> 450
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agcctaagta taagaacaac ctttggggag aaaccatcat ttgacagtga ggtacaattc 240
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tcaagtcaac acatctgtga actcacagac caagttctta aaccactgtt caaactctgc 420
tacacatcag aatcacctgg agagctttac aaactcccat tgccgagggt cgacgcggcc 480
gcgaatttag tag
<210> 451
<211> 501
<212> DNA
<213> Homo sapiens
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ctcttcgcta ttacgccagc tggcgaaagg gggatgtgct gcaaggcgat taagttgggt 120
aacgccaggg ttttcccagt cncgacgttg taaaacgacg gccagtgaat tgaatttagg 180
tgacnctata gaagagctat gacgtcgcat gcacgcgtac gtaagcttgg atcctctaga 240
gcggccgcct actactacta aattcgcggc cgcgtcgacg tgggatccnc actgagagag 300
tggagagtga catgtgctgg acnctgtcca tgaagcactg agcagaagct ggaggcacaa 360
cgcnccagac actcacagct actcaggagg ctgagaacag gttgaacctg ggaggtggag 420
gttgcaatga gctgagatca ggccnctgcn ccccagcatg gatgacagag tgaaactcca 480
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tcttaaaaaa aaaaaaaaa a
                                                                     501
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  <211> 51
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 <221> misc_feature
 <222> (1)...(51)
 <223> n = A,T,C or G
 <400> 452
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                                                                    51
 <210> 453
 <211> 317
 <212> DNA
 <213> Homo sapiens
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 <221> misc_feature
 <222> (1)...(317)
 <223> n = A,T,C or G
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ttcacccana cagcctgttt ctatcctgtt taataaatta gtttgggttc tctacatgca 180
taacaaaccc tgctccaatc tgtcacataa aagtctgtga cttgaagttt antcagcacc 240
cccaccaaac tttatttttc targrgtttt ttgcaacata tgagtgtttt gaaaataagg 300
tacccatgtc tttatta
<210> 454
<211> 231
<212> DNA
<213> Homo sapiens
<400> 454
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taagccacgc cacgctcttg aaggagtctt gaattctcct ctgctcactc agtagaacca 120
agaagaccaa attettetge atcecagett geaaacaaaa ttgttettet aggtetecae 180
ccttcctttt tcagtgttcc aaagctcctc acaatttcat gaacaacagc t
<210> 455
<211> 231
<212> DNA
<213> Homo sapiens
<400> 455
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cattgttccg aatgggcttt ccacaggcta cacacacaaa acaggaaaca tgccaagttt 120
gtttcaacgc attgatgact tctccaagga tcttcctttg gcatcgacca cattcagggg 180
caaagaattt ctcatagcac agctcacaat acagggctcc tttctcctct a
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<211> 231
<212> DNA
<213> Homo sapiens
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cctttttatt tggtgcagct gctagtcagt ccctgactga cattgccaag t
<210> 457
<211> 231
<212> DNA
<213> Homo sapiens
<220>
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<222> (1)...(231)
<223> n = A,T,C or G
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tatttgattt tattagcaat ctctttcaga agacccttga gatcattaag ctttgtatcc 180
agttgtctaa atcgatgcct catttcctct gaggtgtcgc tggcttttgt g
<210> 458
<211> 231
<212> DNA
<213> Homo sapiens
<400> 458
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<211> 231
<212> DNA
<213> Homo sapiens
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gccctgcact gttttccctc caccacagcc atcctgtccc tcattggctc tgtgctttcc 180
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<213> Homo sapiens
<400> 460
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 cccacctccc cacacgcaca cggccagcct ggagcccaca gaagggtcct cctgcagcca 180
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<212> DNA
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<211> 231
<212> DNA
<213> Homo sapiens
<400> 464
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cetgetteag tgactgtgtg cetgtagtee cagetacteg ggagtetgtg tgaggecagg 180
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aggatggcac aatttttgct tgtgttcata atatactcag attagttcag ctccatcaga 180
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<212> DNA
<213> Homo sapiens
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cctgtgcaat caaatattgt ggagaattcc ctagctggag aagtcacaaa gactataggc 180
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tgtgccttaa cagaaggtct tgagattcta agtgggaatc atttcagtga ctgtcatgtg 180
gcatgggtct ctgcccaagc tcgtaatgag actatagcaa ggcggctgtg ggacgtcagt 240
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WO 00/04149 PCT/US99/15838 167

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WO 00/04149 PCT/US99/15838

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